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Symposium on Rheumatic Fever

Introductory Remarks

Needs for Rheumatic Fever Research

COMPLACENCY in medicine is the enemy of progress. That which stands still retrogresses. Research in rheumatic fever has nurtured significant advances and great promise for the future. The decision as to whether we should accept our progress to date or pursue our studies to their ultimate goal, is squarely on our shoulders. Naturally, the ultimate goal is prevention of rheumatic fever and rheumatic heart disease.

What are the remaining needs in rheumatic fever research?

First, there are problems of etiology. Most American physicians accept the concept that the group A beta hemolytic streptococcus is related etiologically to rheumatic disease. The mechanism of this relationship, however, remains in complete obscurity. Many research workers are attempting to extract various fractions from streptococci to find a specific pathogenic factor. None of these probatory studies have provided the answer to this problem. Such factors as sex, age, socio-economic status, environment, climate, crowding, etc., all play an apparent role—but again, the mechanism by which they exert their influence is not known.

Second are problems in diagnosis. In 1944, T. Duckett Jones promulgated the use of certain criteria as a guide to the diagnosis of rheumatic fever. These criteria have been modified recently, and are very helpful in evaluating rheumatic disease. Unfortunately, however, there is no single specific test for rheumatic fever. Furthermore, the major manifestations are seen characteristically with decreasing frequency. While the incidence rate undoubtedly is declining, many cases still occur, but do not conform to the typical syndrome as described in textbooks on the subject. The medical practitioner is confronted with the difficult task, sometimes impossible, of determining whether or not the vagaries of an atypical illness represent rheumatic fever. The need for a specific diagnostic procedure is urgent.

Third, problems in therapy still remain. The past two decades have seen the therapeutic regime for rheumatic fever undergo drastic modification. A prophylactic program has been developed. Antibiotics and steroids have come to the fore. Nonetheless, we have not solved either the prophylactic or the curative phases of rheumatic disease. Breakthrough of both streptococcal and rheumatic infections has been noted during prophylactic regimens which are considered adequate. Concerning the steroids, the storm still rages.

Current concepts and present-day knowledge regarding rheumatic fever are presented in the accompanying symposium. Each of the investigators in the group appreciates the need for more definite information.

Let us then not be complacent! Let us force our research forward. Let us study intensively the cause, the diagnosis and the treatment of rheumatic fever.

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Epidemiology of Rheumatic Fever*

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CONSIDERABLE knowledge about the pathogenesis of rheumatic fever has been accrued in the past quarter of a century. There remain, however, many facets in the development of this disease which are not clear. The correlation of upper respiratory tract infections caused by beta hemolytic streptococci of Lancefield group A and rheumatic fever can scarcely be questioned, although rheumatic fever has never been proven to be an infectious disease with hemolytic streptococci as the sole etiologic agents. A review of the epidemiologic aspects of rheumatic fever is warranted since certain predisposing factors seem to be present frequently.

DEFINITIONS AND TERMS

The "*rheumatic state*," a term introduced by Coburn,[9] refers to all phases of the clinical and pathologic process of rheumatic fever including the stage of inactivity of the disease as well as when it is active. *Active rheumatic fever* is the term used to indicate that the disease is progressing, smoldering, receding or changing. In this phase of the rheumatic state one or more of the following is in evidence: polyarthritis, changing or progressive cardiac findings, Sydenham's chorea, erythema marginatum, subcutaneous nodules, fever, leukocytosis, presence of C-reactive protein, elevation of the erythrocyte sedimentation rate, protein-bound polysaccharide and/or serum mucoproteins, and electrocardiographic evidence of carditis. Laboratory signs of disease activity are always present in active rheumatic fever even though clinical signs of such activity may be absent.

Inactive rheumatic fever is the term used to describe that phase of the rheumatic state which follows complete disappearance of all signs, symptoms, and laboratory evidence of rheumatic activity. *Rheumatic heart disease* is the term utilized to designate clinical evidence of cardiac involvement by the rheumatic process; rheumatic fever may be active or inactive. The term *active rheumatic heart disease* is warranted when rheumatic activity is involved in the form of myocarditis, valvulitis, or pericarditis. However, when organic murmurs of residual valvular damage persist or are discovered in the absence of all signs of active rheumatic fever, the state is designated as *inactive* or *quiescent rheumatic heart disease*.

The nature of the relationship of Sydenham's chorea to rheumatic fever is far from clarified. For the purpose of this discussion we shall consider Sydenham's chorea as a manifestation of the rheumatic state unless otherwise indicated.

INCIDENCE OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Rheumatic fever is not a reportable disease in most communities. Inaccurate diagnosis of this disease alters the reliability of statistical surveys.[66] The incidence of rheumatic fever usually refers to the number of new cases of the disease which have occurred in a period of a year within a given population. The prevalence of patients in various stages of the rheumatic state is a more meaningful guide, since it indicates the proportion of persons in a specific population who are affected in any way by this disease. This includes individuals who are experiencing an episode of rheumatic fever at the time of the study, those with quiescent rheumatic heart disease, and those in whom a definite retrospective history of rheumatic fever is obtained even though the disease is inactive.

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Following an analysis of a survey of 825,000 white families in various states Collins[12] reported that an average of 3.15 persons per 10,000 of all ages developed an attack of rheumatic fever in any one year. In the same study 4.56 per 1,000 children up to the age of 25 years gave histories of having had at least one attack of rheumatic fever. Surveys in recent years show a variable attack rate of rheumatic fever among school children, with figures ranging in some areas from a low of one per 1,000 up to as high as 4 per cent.[11,51] Coburn[10] stated that there were at least a million cases of streptococcal sore throats in Navy personnel during World War II, and that these led to somewhat over 40,000 cases of rheumatic fever with or without rheumatic heart disease. Thus the rheumatic fever attack rate following streptococcal upper respiratory infections was about 4 per cent for these men during that period. The annual occurrence rate of rheumatic fever was 37.8 per 1,000 personnel in 1943 at the Naval Training Center, Farragut, Idaho.[10] The comparable figure for the civilian populations was far less.

In general, however, there has been a marked reduction in the mortality from rheumatic fever in the past 40 years.[84] This trend was evident prior to the advent of antibiotic and chemotherapeutic agents; explanation of this decline in the incidence of rheumatic fever is not apparent. At the present time the death rate for rheumatic fever is but one-sixth of that figure for 1910.[25] The reason for such a reduction is not clear either. It can be estimated that nearly 2,000,000 persons in the United States have already had, or will develop, an attack of rheumatic fever sometime during their life span. Probably half of the 2,000,000 will have residual heart damage, of which over 500,000 will die because of the rheumatic process or some complication developing directly from it.

Mortality figures for rheumatic heart disease are difficult to interpret. In 1954 there were 18,256 deaths due to chronic rheumatic heart disease and 1,297 deaths directly attributed to acute rheumatic fever.[77] Rheumatic patients comprised 0.1 to 5 per cent of the admissions to general hospitals.[34,51] Children's hospitals would be expected to give a somewhat higher figure. Deaths from cardiac disease in 1936 in the age group 5 to 24 years are approximately 1.8 per 10,000 population;[6] the principal cardiac deaths in this age range are due to rheumatic heart disease.

These statistics may not be particularly impressive when compared with death rates from certain other diseases and accidents. However, in considering the magnitude of the problem of rheumatic fever, cognizance must be made of the morbidity associated with the disease, as well as the mortality.[3] The continued medical supervision required for rheumatic patients to prevent recurrences and for avoidance of progressive cardiac damage, places the responsibility for the problem of rheumatic fever on the community in many instances. Frequently, a false sense of security is given when mortality figures alone are observed. The ability of these individuals to be rehabilitated following an episode of rheumatic fever is most often a task best handled by a group of specially trained persons. How are these rheumatic subjects being restored? Are they presenting custodial problems for their society, or are they being rehabilitated to the optimum of their cardiac tolerance? Are prophylactic agents available to rheumatic patients, and are steps being taken to educate them about the imperativeness of prevention of subsequent episodes of streptococcal infection? These are but a few of the salient questions which must be posed concerning the community aspects of rheumatic fever. The prevalence figures for incidence of rheumatic fever or rheumatic heart disease are only partial indicators of the existing problems.

The Role of the Hemolytic Streptococcus in the Etiology of Rheumatic Fever

Clinicians have known for the past 80 years that rheumatic fever follows episodes of tonsillitis. Numerous studies have demonstrated the relationship between infections by beta hemolytic streptococci of Lancefield group A and the subsequent onset of a rheumatic episode.[36,57,61] Outbreaks of rheumatic recurrences were noted in convalescent homes subsequent to culture-proven hemolytic streptococcal tonsillopharyngitis in 1930.[13,70] The latent period from the onset of the sore throat to the development

of rheumatic manifestations varied from 9 to 25 days.

In discussing the epidemiology of rheumatic fever, the role played by beta hemolytic streptococci necessitates consideration of factors concerned with streptococcal infections. The decline in the incidence of rheumatic fever since the turn of the century[67,84] is partly explained by the introduction of antimicrobial agents. This mode of approach to the prevention of rheumatic fever has been directed toward the early treatment of all streptococcal infections in persons who have not experienced an attack of rheumatic fever. In rheumatic individuals, with or without rheumatic heart disease, a program of continuous prophylaxis is also utilized against streptococcal disease and the carrier state.

Epidemiologic Observations: The relationship of epidemics of streptococcal disease, especially sore throats, to rheumatic fever was readily appreciated in 1886.[65] This was further delineated when 30 to 60 per cent of patients with acute rheumatic fever yielded positive cultures for beta hemolytic streptococci.[74] Paul,[51] in 1943, pointed out that epidemics of rheumatic fever occurring in military personnel were characterized by environmental conditions conducive to the spread of streptococcal infection. These included placing together large numbers of susceptible young men and constantly adding new individuals. Personnel are crowded, particularly when sleeping in bunk fashion, usually while there is wet, cold weather.

One of the most impressive studies which has demonstrated the association of streptococcal respiratory infections to rheumatic fever was carried out by Coburn.[10] In a classic document entitled "The Epidemiology of Hemolytic Streptococcus," the incidence of streptococcal infection, scarlet fever, and rheumatic fever in the U. S. Navy during World War II is reviewed. From these observations it appears that the "rheumatogenic factor" of group A streptococci may be a strain characteristic. The biochemical nature of such a rheumatogenic substance is unknown.

Peak incidence of streptococcal infection occurs in the late winter months in the United States and is followed about a month later by the highest incidence of rheumatic fever. Similarly, the low incidence of streptococcal tonsillopharyngitis in late summer coincides with the ebb of rheumatic fever. In regard to the geographic location in the previously mentioned study,[10] the morbidity statistics for rheumatic fever followed those of scarlet fever and tonsillopharyngitis. Considerably more streptococcal disease and rheumatic fever were witnessed in the Naval installations in the northern sections of the country than in those in the southern climate. Occasionally, however, outbreaks of sore throat did occur in southerly located training bases, particularly during winter months, and these were followed by an increased incidence of rheumatic fever. In general, however, training units with little streptococcal disease revealed only a few cases of rheumatic fever.

Because of the astonishingly high incidence of streptococcal disease and rheumatic fever at some of the Naval installations during World War II chemoprophylaxis was initiated with sulfonamides for all personnel. This method reduced the incidence of these diseases very effectively in 1944 at several of the larger Naval training centers.[10] However, sulfonamide-resistant strains of group A beta hemolytic streptococci emerged[14,15,22,64,76,83] with the occurrence of epidemics of scarlet fever and tonsillopharyngitis in 1945 when rheumatic fever became prevalent. No penicillin-resistant strains of group A beta hemolytic streptococci have been reported thus far. Utilization of this antibiotic seems most feasible in the mass prophylaxis of military personnel under epidemic conditions of streptococcal disease.

Types of Streptococci: When rheumatic fever follows hemolytic streptococcal infections the latter are almost invariably in the upper respiratory tract. The complications of streptococcal infections fall into two categories, viz., suppurative and nonsuppurative. The presence of one or more suppurative complications, such as otitis media or cervical adenitis, does not add further to the likelihood of this individual developing rheumatic fever. It is also not clear why, following a streptococcal respiratory infection, some individuals go on to manifest symptoms of rheumatic fever, whereas in others another nonsuppurative complication develops, i.e., glo-

merulonephritis. In contrast to rheumatic fever, some types of group A streptococci, especially type 12, are more prone to be associated with glomerulonephritis; in fact, the toxins of type 12 have produced in rabbits manifestations similar to this renal disease in man. Although some strains have had a higher occurrence rate of rheumatogenic complications than others all strains of group A organisms apparently are capable of being rheumatogenic. Immunity to specific types of group A organisms probably does occur, but the duration of protection is variable. Since there are more than 40 types of group A organisms, and because cross immunity does not seem to enter into the problem,[40] the possibility of challenge by a different type is indeed great. The latter is particularly evident when one considers that the susceptibility of rheumatic individuals to hemolytic streptococci is increased from an overall attack rate of 3 per cent for this complication to approximately 50 per cent after an individual has once entered into the rheumatic state.

Hemolytic streptococci have been classified into immunologically different groups.[40–42] The group A organisms appear to be the bacteria associated with rheumatic fever, although under special circumstances other groups may be capable of producing other diseases in man. Numerous types of group A organisms have been identified by type specific M-proteins which are antigenic factors producing type-specific antibodies.[40] Antistreptolysin and/or antistreptokinase (antifibrinolysin) may be demonstrated in the sera of individuals having had respiratory infections caused by group A organisms which yield antigens stimulating these antibodies. The presence of any or all of these antibodies does not preclude rheumatic fever nor does it indicate that rheumatic fever is active or imminent. Some observers suggest that certain group A streptococci tend to have "rheumatogenic" properties to a greater degree than do others.[10] There seems to be little difference in the antibody formation of rheumatic and nonrheumatic subjects, except in the production of anti-M precipitin (type specific) antibodies which appear sooner and rise more rapidly following streptococcal infection in non-rheumatic individuals.[8,40,73] This suggests that in rheumatic subjects an inadequate response to the streptococcus may permit the tissues of the host to develop the nonsuppurative complication, rheumatic fever. One of the factors which influences the frequency with which rheumatic fever develops is age. The maturing process in some obscure way may affect the immune mechanisms in certain individuals.

Some strains of group A hemolytic streptococci may develop an increased ability to be pathogenic. This feature is not only related to the spread of streptococcal upper respiratory disease, but also to the frequency with which rheumatic fever follows such infections. The latter is probably partly related to the ability of certain strains of hemolytic streptococci to vary in their rheumatogenic properties.

Clinical Evidence: The close association of group A hemolytic streptococcal infections to the development of rheumatic fever is exemplified by the above observations. Rheumatic fever follows in the wake of streptococcal disease, which almost invariably is manifest in the form of upper respiratory disease. However, some doubt remains as to whether rheumatic fever represents a separate entity or proteanly manifest streptococcal disease. A high incidence of scarlet fever in a given population may precede an increased incidence of rheumatic fever. Conditions which are conducive to the propagation of streptococcal disease, such as overcrowding of susceptible individuals, appear fundamental in the development of rheumatic fever which may assume epidemic proportions by virtue of the increased opportunity for complications to follow the streptococcal infections.[4,10] The frequency with which rheumatic fever follows streptococcal tonsillopharyngitis can be markedly reduced by the appropriate and early treatment of the initial infection.[5,7,16,36,37,47,78] Antibiotic therapy directed against streptococci appears to have little effect in arresting the progression of the rheumatic activity once manifestations of acute rheumatic fever have developed. However, treatment with penicillin should be instituted in a patient during the early stages of acute rheumatic fever in order to eradicate the organism in that individual, and thereby avoid smoldering or recurrent streptococcal disease.

No quantitative correlation exists between the severity of the manifestations of the tonsillopharyngitis and the frequency or severity of the subsequent episode of rheumatic activity. Hemolytic streptococci of the same type as those isolated from the nose and throat have been recovered from the hearts of autopsied individuals succumbing to acute rheumatic fever;[13,27,75] however, this is an infrequent and inconsistent finding.

Failure to obtain a history of a streptococcal infection followed by acute rheumatic fever is not uncommon, especially in adults with rheumatic heart disease.[3] In witnessing an acute episode of rheumatic fever the patient frequently denies knowledge of a preceding sore throat with fever; symptoms suggestive of a nonspecific upper respiratory infection may be obtained only upon direct questioning. Unfortunately, too, there are no specific manifestations which would enable one to predict the complication of rheumatic fever, even when a sore throat is present in its typical form.

In summarizing the role played by hemolytic streptococci in the epidemiology of rheumatic fever it appears unquestioned that group A hemolytic streptococcal infections of the upper respiratory tract are in some way connected to the antecedent events which lead up to the clinical features which are called rheumatic fever.[6] This initial infection may be more or less of a trigger mechanism to set off a series of events which subsequently take place. The strongest clinical evidence to support this relationship lies in the observation that certain epidemics of streptococcal tonsillopharyngitis are followed by an as yet unpredictable increase in the incidence of rheumatic fever. Furthermore, in rheumatic outbreaks a retrospective history of streptococcal disease of the nose and throat can be almost always elicited. There seems little doubt then that the group A streptococcus plays the role of a specific, or at least the primary (preparatory or provocative) extrinsic agent in the development of an episode of active rheumatic fever.

Host Susceptibility

Although the frequency with which initial attacks of rheumatic fever follow streptococcal infections varies considerably, an average occurrence rate is probably about 3 per cent.[55,58] If a rheumatogenic property of the streptococcus were the only factor involved in the pathogenesis of this disease, repeated infections in the same susceptible individual would be expected eventually to produce rheumatic fever. As will be brought out later, rheumatic fever tends to recur in families and the increased incidence of the disease cannot be explained solely by the increased number of streptococcal infections within the family unit. Recurrent attacks of rheumatic fever are preceded by a new streptococcal infection in almost all instances, and the attack rate increases from the above mentioned 3 per cent to 50 per cent or greater.[7,31,32,47] In evaluating the epidemiologic aspects of 757 cases of rheumatic fever which occurred in a military population, Quinn[54] reported that one-fourth of the patients were able to give a retrospective history of already having experienced at least one attack of rheumatic fever. However, infections with group A hemolytic streptococci are not followed invariably by another attack of rheumatic fever in rheumatic subjects.

Other factors, such as the response of the host, which may be interpreted as an immune reaction, and his susceptibility to the effects of the streptococci, which might be considered rheumatogenic, are important facets in the pathogenesis of rheumatic fever.[10] An accelerated response of antibody to streptococcal disease in rheumatic subjects has already been brought out.[17] Stetson[71] carried out studies which again demonstrated that rheumatic individuals have a significantly higher antistreptolysin-O titer response to streptococcal infections when compared to nonrheumatics. In groups of patients with especially high peak titers of antistreptolysin-O, the incidence of rheumatic fever is also increased as compared to groups of individuals with low peak titers for this antibody.[60] However, the conclusion that a positive relationship exists between the level of antibody early in streptococcal disease and the subsequent development of rheumatic fever is not warranted.

Studies designed to yield information about the host response to beta hemolytic streptococcal infections in the experimental animal are to a great extent limited, since as yet man appears to

be the only animal in which the typical clinical and pathologic picture of rheumatic fever becomes manifest. The generalized Schwartzman reaction has been produced in the American Dutch rabbit, utilizing products of group A streptococcal origin, such as streptolysin-O.[79] This offers another experimental approach toward answering some of the many unanswered questions about the nature and pathogenesis of rheumatic fever, since certain of the mechanisms in the development of rheumatic fever in man are similar to those observed following the generalized Schwartzman phenomenon in rabbits, particularly from a histologic viewpoint.

The state of susceptibility of the host to streptococcal infections and rheumatic fever is uncertain. Whether this is primarily connected with the immune mechanism or an alteration of biochemical function is unknown. It is clear, however, that attacks of rheumatic fever may occur in a susceptible host after he has an infection of the upper respiratory tract caused by a strain of beta hemolytic streptococci of Lancefield group A, which has so-called rheumatogenic properties.[10]

The Factor of Age in Rheumatic Fever

The epidemiologic aspects of rheumatic fever must encompass the factor of age. The disease seems to be predominately one occurring in childhood and early adulthood with the age period of mid-childhood being the one of greatest incidence of initial attacks. The highest incidence occurs between 5 and 12 years, with more than 50 per cent of all first attacks occurring prior to the age of 15 years. Only 25 per cent of all cases, both initial and recurrent, manifest themselves after the age of 30 years. The mean peak of initial attacks is 7 years.[51,81] Primary attacks predispose to subsequent bouts of rheumatic fever so that episodes of the disease continue to be common in late adolescence and early adult life. Over 90 per cent of all cases of rheumatic fever occur after the age of 4 years, with the incidence under one year of age approaching zero.[67] Hedley[34] reported 0.7 per cent of 2,324 patients having their initial episode of rheumatic fever under the age of two years, and only 8.4 per cent under the age of five years. Prior to 1930 the peak of the incidence was in the second decade, whereas subsequently there has been a lowering of this maximum incidence into the first decade;[51] the explanation of this is not completely evident.

The prevalence of rheumatic fever depends upon the opportunity for exposure of susceptible persons to hemolytic streptococci. Rural families who are susceptible might move to an urban area where streptococcal disease is rampant. This would set the stage for the development of rheumatic fever and therefore the family members would pass from a situation of relatively limited opportunity for the development of this disease to one which may be very high; this thereby appears to lower the age of onset of initial attacks.[51] Obviously, environmental factors may readily influence the age at which initial attacks occur.

The infrequency of occurrence of rheumatic fever under the age of five years and its rarity below three years may be interpreted as lending to the concept of tissue sensitization which, in turn, requires the process of maturation. Some of us like the idea of conditioning of tissue similar to the development of patterns of response of the host in streptococcosis. The increased prevalence of rheumatic fever in five and six-year-olds, as compared to the incidence in preschool ages, may be explained only in part by the possible added exposure of the children to streptococcal disease in school. Infections with group A streptococci manifest themselves differently in young children and infants.[53] Infections of the respiratory tract caused by hemolytic streptococci occur frequently in young children. However, nonsuppurative complications of streptococcal disease are extremely uncommon in this age group.[53,60] It is not clear whether the rapid development of apparent increased susceptibility to rheumatic fever is an expression of maturation of tissue response related to the immune mechanism or a result of tissue changes occurring from repeated bouts of streptococcal infection. The process of aging also allows time to elapse for repeated exposure to these infections. Study of the antibody response following streptococcal infections in childhood suggests that there is immunologic evidence that recurrent challenges by streptococci are of more importance than is the factor of aging alone.[59]

In summary of the discussion of the factor of age on rheumatic fever, certain persons pass through a phase of relatively low susceptibility into an age group (5 to 16 years) during which there is a sudden increase in the incidence of rheumatic fever. Initial and recurrent attacks of the disease become less frequent as further aging takes place, so that beyond the fifth decade acute episodes of rheumatic fever are again as uncommon as they were under the age of five years. The influence of age on the incidence of rheumatic fever remains unexplained; it is probably related to local tissue response, the host immune mechanism, and repeated exposure to streptococcal infections.

Influence of Race and Sex on the Development of Rheumatic Fever

To evaluate racial differences in rheumatic subjects one is faced with uncertainty, because factors other than race are also variable. Some of these factors are socio-economic and environmental, whereas others are related to the racial differences in the distribution of patients in inpatient and outpatient services. In spite of these difficulties several variations in racial susceptibility are worthy of comment.

People of Irish extraction residing in the New York City area seem to acquire rheumatic fever more readily than persons of other nationality background.[51] This observation is influenced by factors of crowding and enhancement of the spread of streptococcal disease. The recent immigration of this particular group of people may play a role, as this may entail the movement of a potentially susceptible population into an environment conducive to the development of rheumatic fever.

In Negroes the attack rate of rheumatic fever is not increased, as compared to whites. However, the mortality from this disease appears to be somewhat higher among Negroes. The peak of the initial attack rate for rheumatic fever in Negroes has been observed to fall between the tenth and the fourteenth year by Hedley[33,34] in Philadelphia, whereas white children between the fifth to the ninth year of age appear to be the most susceptible. Ash,[2] also working in Philadelphia, noted that 83 per cent of the rheumatic individuals were white and 17 per cent Negro in a pediatric clinic where the general distribution of Negroes and whites was about equal. However, it was observed in this same study that after the Negroes developed rheumatic fever they seemed to handle the disease less readily and the frequency and degree of residual heart damage was increased.[2] The personal experience of the authors has been in essential agreement as well. Rheumatic fever and rheumatic heart disease are more likely to be fatal in Negroes than in whites, as suggested by the mortality statistics.[2,34] As yet, no conclusive evidence is available to demonstrate racial susceptibility to rheumatic fever. However, when the hereditary aspects of this disease are considered, racial predisposition and resistance remain as possible factors influencing epidemiology.

Sydenham's chorea has occurred nearly twice as commonly in females as in males. Under the age of 13 years there is a greater tendency for rheumatic fever to develop in girls than boys. However, in late adolescence and early adulthood the disease occurs slightly more often in males than females. This might be influenced by the increased rate of rheumatic fever in certain military installations in the older age group. The slight increased incidence among girls under the age of 13 years might be explained in part by the apparent predilection for chorea to occur in females.

In a recent study 76 of 118 rheumatic patients on a specific prophylactic program were girls.[20] There was no selection of patients in this series, although occult factors may have influenced the sex distribution. Of 696 children observed from 1916 to 1935, 387 were girls and 309 boys; the mean age of onset of the rheumatic process appeared one year later in girls than boys.[81] In a series of 91 patients admitted to the Pediatric Service of the University of Texas Medical Branch over a 5-year period 55 per cent were females and 45 per cent were males.[43]

Although these figures suggest a predilection of rheumatic disease for females, this distribution is probably not statistically significant. Certainly there is no difference in the amount or degree of residual heart damage between the sexes. In actuality there is no apparent reason at this state of knowledge to explain why a sex

difference should exist with respect to susceptibility or resistance to rheumatic fever.

Hereditary and Familial Aspects of Rheumatic Fever

The wealth of clinical data collected over the past 25 years compels one to draw the conclusion that a certain familial incidence of rheumatic fever exists. Evaluation of the genetic aspects strongly suggests that this familial incidence is partially explained by a hereditary susceptibility or predisposition.[80,82] The exact genetic relationships are not completely clear, although the mechanism of heredity has been suggested to be a single autosomal recessive gene.[62,81,82] However, the factor of penetrance plays a role as do environmental aspects. Penetrance in rheumatic fever may be defined as the percentage of hereditary susceptible individuals who manifest the trait.[81] If this penetrance is incomplete, the frequency with which rheumatic fever occurs within a family group could be governed by the opportunity for exposure to streptococcal disease, the geographic location of the residence, and by socio-economic factors.

Siblings of rheumatic children are more prone to develop rheumatic fever than are children who do not have brothers and sisters with the disease. Individuals with histories of close relatives affected by rheumatic fever also have an increased predilection for this disease. The offspring of rheumatic parents likewise have a greater likelihood of developing rheumatic fever than do the children of nonrheumatic parentage.[72] In a given family, after one child has had rheumatic fever, the possibility of subsequent siblings being susceptible is one in four; when one parent is also rheumatic the chances may increase to one in two.[80,81] Of 38 families of lower income in New York City, with four or five children per family, Wilson[81] observed that in three of the families with both parents rheumatic all 13 children were also rheumatic. Paul,[51] studying the familial aspects of rheumatic fever in 122 families, concluded that 3 to 4 per cent of offspring of nonrheumatic parents may develop rheumatic fever; however, with one child rheumatic 10 per cent of the siblings also will be rheumatic, under the same circumstances; finally, in a family of a rheumatic child with one or both parents who have had rheumatic fever, 25 per cent or greater of his siblings may be expected to have the disease. Further observations have been made more recently by Stevenson and Cheeseman,[72] who noted that six of 51 women with rheumatic heart disease produced nine children who subsequently developed rheumatic fever and 26 who did not, giving an affected rate of 26 per cent. Reed[63] has pointed out, however, that 45 of these mothers with damaged hearts produced no affected children, which gives an overall rheumatic fever affected rate of 6 per cent. Apparently 12 per cent of rheumatic mothers can be expected to produce one or more children who will develop rheumatic fever.

In summarizing 246 sets of rheumatic twins from twelve author sources, Reed[63] noted that of 113 identical twin sets rheumatic fever was present in both children in 32, whereas the disease was present in both fraternal twins in only 10 of 123 sets. Sixty-three families involving 126 siblings of rheumatic children have been studied recently at the Children's Convalescent Center. Over a period of four years, three initial attacks of rheumatic fever have been observed to occur in these previously unaffected brothers and sisters.[28–30] An evaluation of hereditary and environmental factors in the development of rheumatic fever at La Rabida Sanitarium has indicated that the incidence of rheumatic fever was significantly higher in families in which one or both parents had had the disease.[18] However, the pattern of susceptibility may be said to follow a simple autosomal recessive gene inheritance only when both parents had had rheumatic fever.[18] Occurrences of rheumatic fever among school age siblings have not enhanced the development of the disease in the preschool age siblings.[51] Although explosive epidemics of rheumatic fever among siblings is not the usual mode of spread, group A hemolytic streptococcal infections occurring in a susceptible family often may be followed by episodes of rheumatic fever in more than one member of the family.

The inherited relationship between parental rheumatic fever and that of the siblings appears to be well established. The tendency to inherit susceptibility to rheumatic fever seems evi-

dent. Because such a trait as susceptibility to rheumatic fever is influenced by environmental factors, it is difficult to determine whether the basic heredity is low penetrance of a dominant trait, or a relatively high penetrance of a recessive one.[63] Therefore, it behooves the practicing physician to investigate, examine and follow the entire immediate family of a rheumatic child.

The Roles of Environment, Climate and Seasonal Variation in the Development of Rheumatic Fever

In a discussion of the epidemiology of rheumatic fever the factors of environment, climate and seasonal variation must be considered. The manner by which they influence the pathogenesis of rheumatic fever appears to be primarily through the roles which they play in the epidemiology of streptococcal infections.

There is a lack of unanimity in the medical literature concerning the influence of low income upon the attack rate of rheumatic fever. No positive correlation exists according to Friedberg.[23] However, in Australia a study indicated a definite association between low income and the incidence of rheumatic fever.[35] In determining the economic status of families in the United States, Collins[12] observed that the incidence of rheumatic fever among families on relief was twice that of families with an annual income over $3,000. In evaluating conditions within the family environment which might alter the attack rate of rheumatic fever, Diamond[18] concluded that only a totally unfavorable environment influenced the incidence of this disease. When factors such as damp, dark living quarters and inadequate clothing or insufficient food (either in quality or quantity), were considered separately, no significant difference in the attack rate of rheumatic fever was observed. The explanation of why this aggregate of totally unfavorable environmental circumstances alters the attack rate of rheumatic fever is not clear unless answered by the enhancing effect of these factors on the spread of streptococcal upper respiratory infections and their early and adequate therapy. Crowding of members of families within their homes indeed may increase the incidence of rheumatic fever, as crowding affects members of units in certain military installations or situations.[4,10] The circumstances created in crowded areas, usually urban, are conducive to the propagation of streptococcal disease. Therefore, the incidence of rheumatic fever tends to be increased in poverty-stricken areas, where crowding is present. Then, too, the likelihood of inbreeding of the factor of susceptibility to rheumatic fever might be greater than that in families of a higher socio-economic level.

The season of the year also relates to the incidence of rheumatic fever with a peak being reached in late winter and early spring.[50] A waning is evident in late summer with the lowest incidence in late fall.[21,24,26] The seasonal distribution curve for the incidence of rheumatic fever is similar to that for streptococcal infections, with the high and low points running about a month (lag phase) earlier in the latter.[67] Epidemics of the disease may occur during the winter and spring months when crowding of susceptible individuals prevails.

Climate is associated with rheumatic fever in that the disease has a greater incidence in the temperate zones.[52,69] Since scarlet fever occurs three times as frequently in the northern part of the United States as in the southern,[68] a higher attack rate for rheumatic fever in the colder areas may be expected.[67] Again, however, the influence of the colder climate upon the incidence of rheumatic fever is primarily related to its enhancement of certain factors which lead to the spread of streptococcal disease.

The Role of Recurrences in Epidemiology

Although the frequency with which the initial attack of rheumatic fever follows group A streptococcal infections varies considerably, a figure of 3 per cent is accepted generally.[55,58] Attacks of rheumatic fever are not followed by immunity to subsequent episodes of the disease. Actually, an increased susceptibility to streptococcal infections and rheumatic fever appears to prevail, such that subsequent attacks of the disease may reach a recurrence rate of 50 to 70 per cent in rheumatic subjects.[7,31,32,47] Although treatment of streptococcal infections in rheumatic individuals reduces this recurrence rate of rheumatic fever,[46,47] the utilization of a proper program of prophylaxis against strepto-

coccal disease almost abolishes the possibility of subsequent episodes of rheumatic fever.[19,20,38,39,44,45,56] In certain ways it seems somewhat unique that the disease does not recur more frequently in rheumatic subjects following streptococcal upper respiratory infections.

From the studies on persons who have had one or more attacks of rheumatic fever, a number of observations can be made. The possibility that streptococcal infections occur more frequently in subjects who had had rheumatic fever has not been established in fact. A recurrence of the disease almost always is preceded by a new and recent upper respiratory infection caused by group A streptococci. It appears then that either the host tissues become further sensitized to the certain properties of group A streptococci, which may prove to be rheumatogenic, or that parts of the immune mechanism develop improperly or actually fail in these rheumatic susceptible individuals. The sequence of events involved in the development of a recurrent attack of rheumatic fever can be prevented by not allowing group A streptococcal organisms to reinfect the susceptible host. Once a susceptible host has been reinfected a chain of events may be initiated which lead to rheumatic recurrence, even though therapy is directed toward eradication of the streptococcal infection (after the chain reaction is under way).

Summary

Certain facets of the epidemiology of rheumatic fever are not clear. The correlation of group A beta hemolytic streptococcal infections and rheumatic fever is established; in all probability this is the specific etiologic agent in rheumatic fever. The latter then may prove to be a clinical manifestation of a certain phase (nonsuppurative and late) of streptococcal infection, rather than a disease entity in itself. In numerous respects the epidemiology of rheumatic fever mimics that of streptococcal infections.

Some conditioning of tissue by infection, especially through antigen-antibody interaction or hypersensitivity, is probably involved in the basic pathogenesis of rheumatic fever.[1,48,49] Most group A streptococci very likely furnish the antigenic stimuli concerned in the development of this pathologic process and this may prove to be their rheumatogenic property. The response of the immunologic mechanisms of the host governs in some way the initiation and progression of the histopathologic changes which occur. Alterations in the immune response are probably precursors to the evolution of events in the pathogenesis of rheumatic fever.

Other factors may play an important part in the epidemiology of this disease. The inherited susceptibility to rheumatic fever has been emphasized. The influence of age on the attack rate of rheumatic fever may reflect only the stage of maturity of the immune mechanism of the host. Environmental factors appear to affect primarily the epidemiology of rheumatic fever only as they influence conditions which enhance the spread of streptococcal infections, particularly in streptococcal epidemics. The variability of host factors involving susceptibility and resistance to streptococci, most of which may prove to be "rheumatogenic," make it exceedingly difficult to clarify the role of these factors in the epidemiology and pathogenesis of rheumatic fever. However, to set the stage for the possible development of rheumatic fever a susceptible individual must have been challenged by one of the various strains of group A streptococci. Whether or not a sequence of events follows which leads to rheumatic fever is dependent upon a number of variable and unknown factors.

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The Clinical Picture of Rheumatic Fever*

Diagnosis, Immediate Prognosis, Course, and Therapeutic Implications*

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THE GENERAL purpose of the studies to be reported here is to present the clinical picture of rheumatic fever in initial attacks as it has been observed during recent years at the House of the Good Samaritan. In particular, an attempt will be made to answer the following three sets of questions:

(1) What is the frequency of the principal manifestations of rheumatic fever? How do these manifestations contribute to diagnosis, and what is their significance in regard to the more immediate prognosis?

(2) What is the clinical course of rheumatic fever in its initial attack? When carditis de-

TABLE I

Incidence of Principal Manifestations of Rheumatic Fever in 457 Initial Attacks, Exclusive of Cases of Pure Chorea

Manifestations	Patients admitted 1941–51		Patients selected for therapy studies 1952–55		Total	
	Cases	%	Cases	%	Cases	%
Significant murmurs	156	51	84	55	240	53
Pericarditis	19	6.3	10	6.5	29	6.3
Congestive heart failure	21	6.9	15	9.8	36	7.9
Prolonged P-R interval	80	26	35	23	115	25
Subcutaneous nodules	29	9.5	25	16	54	12
Erythema marginatum	28	9.2	20	13	48	11
Chorea (exclusive of pure chorea)	44	14	17	11	61	13
Fever	273	90	132	86	405	89
Elevated sedimentation rate	273	90	148	97	421	92
Fever and/or elevated sedimentation rate	293	96	149	97	442	97
Antistreptolysin-O titer of 400 units or more	247	81	129	84	376	82
Joint pain	279	92	133	87	412	90
Syndrome of joint pain, fever and/or elevated sedimentation rate, and elevated antistreptolysin-O titer	225	74	113	74	338	74
Total cases	304		153		457	

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velops, how soon do murmurs indicative of heart damage develop? How long do signs of active rheumatic fever last?

(3) What is the implication of these clinical findings in regard to the therapy of rheumatic fever?

The data to be presented have come entirely from our own observations at the House of the Good Samaritan. No attempt will be made in the present communication to review the medical literature nor to relate our findings to those reported by others.

Clinical Material

The clinical material utilized for this study was composed of two groups of patients. The first group was made up of all patients admitted to the House of the Good Samaritan between 1941 and 1951 who met the following criteria: all were under the age of 17 years; all were in their initial attack of rheumatic fever on admission and did not experience any recrudescence of rheumatic fever while under observation; and none received appreciable amounts of antirheumatic therapy. The total number of patients in this group was 337. Of these, 33 had so-called pure chorea and 304 presented other stigmata of rheumatic fever, with or without chorea. The second group was composed of 153 patients selected for various therapeutic studies during the period from 1952 to 1955. None of these patients had pure chorea; all of them were under 17 years of age and were in their initial attack of rheumatic fever.

The Principal Manifestations of Rheumatic Fever: Frequency, Diagnostic Significance and Prognostic Importance

There is reason to believe that early treatment of rheumatic fever with drugs that suppress rheumatic inflammation may contribute to the prevention or reduction of the heart damage that so often results from this disease. Such prompt treatment depends on early diagnosis, and, since there is no specific test for rheumatic fever, diagnosis rests upon an evaluation of the various clinical and laboratory manifestations of rheumatic fever.

Table I shows the incidence of the principal manifestations of rheumatic fever observed in 304 initial attacks among patients admitted to the House of the Good Samaritan between 1941 and 1951 and in 153 additional initial attacks in patients selected for therapeutic studies between 1952 and 1955. The combined data for the total of 457 attacks are recorded in the last two columns of the table. Cases of so-called pure chorea have been excluded from this analysis.

The incidence of significant murmurs observed at the House of the Good Samaritan among patients with various manifestations of rheumatic fever and combinations of manifestations is shown in Table II. For these analyses, which indicate the frequency of cardiac damage, the combined series of 457 patients has been utilized. As in Table I, cases of pure chorea have not been included in Table II.

TABLE II

Incidence of Significant Murmurs Observed in 457 Patients with Various Manifestations of Rheumatic Fever

Manifestation	Patients with manifestation (number of cases)	With significant murmurs	
		Cases	%
Pericarditis	29	28	97
Congestive heart failure	36	36	100
Prolonged P-R interval	115	62	54
Subcutaneous nodules	54	49	91
Erythema marginatum	48	33	69
Chorea (exclusive of pure chorea)	61	40	66*
Fever	405	205	51
Elevated sedimentation rate	421	223	53
Fever and/or elevated sedimentation rate	442	229	52
Antistreptolysin-O titer of 400 units or more	376	197	52
Joint pain	412	205	50
Syndrome of joint pain, fever and/or elevated sedimentation rate, and elevated antistreptolysin-O titer	338	170	50
Total cases	457	240	53

* If cases of pure chorea were included, the incidence of significant murmurs in all patients with chorea would be 30 per cent.

SIGNIFICANT MURMURS

The most common and generally the earliest clinical signs of carditis in acute rheumatic fever are significant murmurs. Although rheumatic myocarditis may play a role in the production of murmurs, the presence of significant murmurs usually points to involvement of the valves. The early lesions are always those of regurgitation (insufficiency), and the valves that are practically always involved are the mitral and/or the aortic valve. Clinically detectable signs referable to the tricuspid and pulmonic valves are almost never encountered during the early weeks or months of initial attacks of acute rheumatic fever.

Mitral regurgitation is usually indicated by the presence of a long, blowing, systolic murmur that is maximum at the apex, where its intensity is at least "moderate" (grade 3) or "slight" to "moderate" (grade $2^1/_2$). The murmur, which sometimes includes very high pitched (squeaky) components, often masks the mitral first sound. Not infrequently a significant apical systolic murmur is accompanied by a low-pitched (rumbling) mid-diastolic murmur, but this latter auscultatory finding when present during early acute rheumatic fever is never indicative of mitral stenosis.

The pathognomonic sign of *aortic regurgitation* is a blowing, diminuendo, diastolic murmur which immediately follows or replaces the second heart sound and which is heard best at either the upper right sternal border or, more commonly, along the mid left sternal border. Although it sometimes may be so faint that it is detectable only by using a careful auscultatory technic, it has definite duration and extends at least one-third of the way or more through diastole.

In the present study significant murmurs were detected in 51 per cent of the patients with initial attacks observed between 1941 and 1951 and in 55 per cent of the patients with initial attacks selected for the therapeutic studies. In the combined group the incidence of significant murmurs was 53 per cent (Table I).

Of those patients with significant murmurs the auscultatory signs were those of mitral regurgitation alone in 71 per cent, mitral and aortic regurgitation in 22 per cent, and aortic regurgitation alone in 7 per cent.

TABLE III

Incidence of Pericarditis in Patients with Various Manifestations

	Total cases	With pericarditis	
		Cases	%
All patients with initial rheumatic fever	457	29	6.3
All patients with significant murmurs	240	28	12
Patients with significant murmurs and prolonged P-R interval	62	9	14
Patients with significant murmurs and nodules	49	12	24
Patients with significant murmurs and erythema marginatum	33	7	21

Significant murmurs are of prime importance in rheumatic fever both in regard to diagnosis and prognosis.

From the point of view of diagnosis, the presence of a significant murmur, if characteristic of that associated with rheumatic valvular involvement, almost always indicates that the patient has or has had rheumatic fever. However, since valvular involvement may be a residual of an attack of rheumatic fever that occurred some years previously, the mere presence of a significant murmur does not necessarily indicate that the rheumatic process is active. For a murmur to be diagnostic of active rheumatic fever, there should be good evidence that the murmur has developed recently. Furthermore, when a murmur is due to active rheumatic fever, elevation of the erythrocyte sedimentation rate and one or more of the other manifestations listed in Table I are almost always present.

In regard to the interpretation of murmurs it is important, of course, to differentiate those due to rheumatic heart disease from physiologic (innocent) systolic murmurs and from organic murmurs caused by other conditions such as congenital cardiac defects, endocardial fibroelastosis, myxoma of the heart, and syphilitic aortitis.

From the point of view of prognosis, significant murmurs are obviously of great importance since they indicate the presence of cardiac damage. Although congestive heart failure, cardiac enlargement, and pericarditis are better indicators of serious heart involvement than is the loudness of murmurs, these three manifestations are rarely observed in rheumatic fever in the absence of murmurs. Thus, in the present study all of 36 patients with congestive failure and all but one of 29 patients with pericarditis also had significant murmurs.

PERICARDITIS

This cardiac sign, recognized by the presence of a characteristic pericardial friction rub, occurred in 29 patients, or 6.3 per cent of the total of 457 patients in their initial attack of rheumatic fever. Since all but one of these 29 patients also had significant murmurs, and since there were a total of 240 patients with significant murmurs, the incidence of definite pericarditis among those with rheumatic valvular involvement was approximately 12 per cent (Table III).

The infrequency with which pericarditis occurs in the absence of significant murmurs (1 out of 29 in this series) makes it somewhat unusual for a diagnosis of rheumatic fever to be dependent upon the detection of this sign. However, occasionally murmurs are completely or partially masked by a loud pericardial friction rub, and under these circumstances recognition of the presence of pericarditis may have considerable diagnostic importance. Furthermore, a definite friction rub in a patient with signs of rheumatic valvular involvement usually is reliable evidence that the rheumatic process is active.

In our experience pericarditis is generally a sign of fairly severe active rheumatic carditis. Consistent with this impression is the high incidence (97 per cent) of signs of valvular involvement in the 29 cases reported here (Table II) and the fact that 46 per cent of patients with both pericarditis and significant murmurs also had congestive heart failure (Table IV). In this connection it is also noteworthy that, although there were only five deaths in the group of 304 initial attacks observed between 1941 and 1951, three of the fatal cases were patients with pericarditis.

CONGESTIVE HEART FAILURE

Signs of congestive failure were observed in 36 or 7.9 per cent of the 457 patients with initial rheumatic fever (Table I). Since all of those with heart failure also had significant murmurs (Table II), the incidence of congestive failure among the 240 patients with significant murmurs and active rheumatic fever was 15 per cent (Table IV).

TABLE IV

Incidence of Congestive Heart Failure in Patients with Various Manifestations

	Total cases	With congestive failure	
		Cases	%
All patients with initial rheumatic fever	457	36	7.9
All patients with significant murmurs	240	36	15
Patients with significant murmurs and pericarditis	28	13	46
Patients with significant murmurs and prolonged P-R interval	62	11	18
Patients with significant murmurs and nodules	49	16	33
Patients with significant murmurs and erythema marginatum	33	4	12

Congestive heart failure developing in the course of active rheumatic fever is an important prognostic sign, indicative of severe carditis. Thus in five (24 per cent) of 21 patients with congestive failure in the 1941–51 series of cases the initial attack of rheumatic fever ended fatally.

From a diagnostic point of view, congestive failure in young people, especially children, with rheumatic heart disease is significant in that it often indicates that the rheumatic process in the heart is still active. On the other hand, congestive failure rarely occurs as an isolated sign of rheumatic involvement of the heart. Therefore, considerable caution should be used in

making a diagnosis of rheumatic heart disease (active or inactive) on the basis of congestive failure when significant murmurs and signs of pericarditis are both absent.

PROLONGATION OF THE P-R INTERVAL

The P-R interval of the electrocardiogram was accepted as being abnormally long when it exceeded 0.20 sec or when it was between 0.18 and 0.20 sec and also at least 0.02 sec above the upper limits for age and heart rate observed in our study of 506 normal electrocardiograms.[1]

The frequency of a prolonged P-R interval, when so defined, was observed to be 26 per cent for the 1941–51 series of initial attacks of rheumatic fever and 23 per cent for the initial attacks included in the therapeutic studies. For the combined group the incidence was 25 per cent (Table I).

Since many infectious diseases as well as a variety of organic cardiac conditions may cause prolongation of the P-R interval, this finding is by no means specific for rheumatic fever. On the other hand, the incidence of an abnormally long P-R interval in rheumatic fever is considerably greater than that observed in other diseases and, therefore, this electrocardiographic manifestation has considerable importance as a confirmatory sign in the diagnosis of rheumatic fever.

Prognostic Importance: In order to determine the significance of prolongation of the P-R interval in regard to immediate prognosis, the 80 cases of a long P-R interval observed between 1941 and 1951 (Table I) were subjected to further analysis. From the results of this analysis, which are shown in Table V, it is evident that there was no difference in the frequency with which P-R intervals of various abnormal durations were observed among 156 patients with rheumatic valvular involvement (indicated by significant murmurs) and among 148 patients without signs of valvular involvement. Hence, although prolongation of the P-R interval presumably is indicative of rheumatic inflammatory changes in the myocardium, the finding has little, if any, significance in regard to the development of valvular damage.

This conclusion is supported by the results of a preliminary follow-up study of 106 of the 148 patients in the 1941–51 series who did not have significant murmurs during hospitalization.[2] Over an average period of 8.5 years of observation (range 5 to 15 years) signs of valvular damage developed in 4 (14 per cent) of 28 patients who had had a long P-R interval and in 8 (10 per cent) of 78 patients whose P-R interval had been within normal limits.

Finally, the lack of appreciable prognostic importance of a prolonged P-R interval is indicated by the fact that the incidence of congestive heart failure and of pericarditis in patients with significant murmurs and a long P-R interval was only slightly greater than the incidence of these two manifestations among all patients with significant murmurs (Tables III and IV).

SUBCUTANEOUS NODULES

The incidence of this manifestation was 9.5 per cent in patients with initial attacks of rheumatic fever observed between 1941 and 1951 and 16 per cent in the patients with initial rheumatic fever selected for therapeutic studies. For the combined group the incidence was 12 per cent (Table I). Forty-nine (91 per cent) of the 54 patients with nodules also had significant murmurs during their period of observation at the House of the Good Samaritan (Table

TABLE V

Duration of Abnormal P-R Intervals in 156 Patients with Significant Murmurs (RHD) and in 148 Patients without Significant Murmurs (PRHD). Data from Series of Initial Attacks Observed between 1941 and 1951

Duration of P-R interval	Number of patients with abnormal P-R interval		
	In 156 patients with RHD	In 148 patients with PRHD	In total of 304 patients
More than 0.24 sec	4	6	10
0.21–0.24 sec	9	9	18
0.20 sec	15	9	24
0.19 sec	6	2	8
0.18 sec	10	10	20
Total with prolonged P-R	44 (28%)	36 (24%)	80 (26%)

II). Thus, the incidence of nodules in the 240 patients with rheumatic valvular disease and active rheumatic fever was 20 per cent.

In all but one of the 5 patients with nodules who did not have significant murmurs the number of nodules was small (one or two). These findings are consistent with our general experience that multiple nodules in rheumatic fever almost invariably are accompanied by signs of rheumatic valvular involvement.

Prolongation of the P-R interval of the electrocardiogram also showed a definite relation to nodules, although not to the same extent as did significant murmurs. Thus the incidence of a long P-R interval was 41 per cent for all patients with nodules and also 41 per cent for patients with both significant murmurs and nodules in contrast to an incidence of 25 per cent for the total group of initial attacks and 26 per cent for all patients with significant murmurs (Table VI).

The correlation of nodules with both signs of valvular involvement and myocardial changes responsible for prolongation of the P-R interval is of considerable interest, especially since valvular involvement and prolongation of the P-R interval show only slight, if any, correlation with each other.

TABLE VI

Correlation of Subcutaneous Nodules and Erythema Marginatum with Prolongation of the P-R Interval

	Total cases	With prolonged P-R	
		Cases	%
All patients with initial rheumatic fever	457	115	25
All patients with significant murmurs	240	62	26
All patients with subcutaneous nodules	54	22	41
Patients with all subcutaneous nodules and significant murmurs	49	20	41
All patients with erythema marginatum	48	16	33
Patients with both erythema marginatum and significant murmurs	33	10	30

Diagnostic Value: The close association of definite rheumatic heart disease with subcutaneous nodules confers a high degree of diagnostic significance on the latter manifestation of rheumatic fever. At the same time it must be remembered that nodules which are clinically indistinguishable from those of rheumatic fever may occur in rheumatoid arthritis and in other collagen diseases and that, therefore, the subcutaneous nodule can not be accepted as a specific sign of rheumatic fever.* Furthermore, it is to be noted: (1) Nodules are a relatively late manifestation which rarely develop in rheumatic fever patients who have been ill less than three weeks. (2) The significant murmurs which usually are evident in patients with nodules indicate the presence of rheumatic heart disease and thus point to the possibility of active rheumatic fever. For these reasons a diagnosis of rheumatic fever, especially an early diagnosis, commonly does not depend upon detection of subcutaneous nodules. Most often the diagnostic role of subcutaneous nodules is that of a confirmatory sign.

In our experience nodules have been found to be of especially diagnostic value under the following two circumstances:

(1) If a patient with multiple nodules is found to be entirely free of signs of cardiac involvement, there is a good possibility that the patient is suffering from rheumatoid arthritis or some other collagen disease rather than rheumatic fever.

(2) If a patient with definite rheumatic heart disease is found to have subcutaneous nodules, it is almost certain that the patient also has active rheumatic fever rather than bacterial endocarditis or some other complicating disease.

Prognostic Importance: From the point of view of immediate prognosis, the importance of subcutaneous nodules is indicated by the high incidence (91 per cent) with which signs of valvular damage occurred in the 54 patients with this manifestation. This incidence figure contrasts strikingly with the figure of 47 per cent for

* Nodules of rheumatoid arthritis may occur in children but are encountered most often in adults. Contrariwise, nodules of rheumatic fever may occur in adults but are seen most often in children.

the rheumatic fever patients who did not have nodules and the figure of 53 per cent for the entire series of 457 patients.

The seriousness of subcutaneous nodules is shown further by the fact that congestive heart failure and pericarditis occurred about twice as often in patients with nodules and significant murmurs as in the entire group of 240 patients with significant murmurs. Thus the frequency of congestive failure was 33 per cent among patients with murmurs and nodules and only 15 per cent in the entire group of patients with heart murmurs (Table IV), whereas the corresponding frequency of pericarditis in these same groups was 24 per cent and 12 per cent, respectively, (Table III).

ERYTHEMA MARGINATUM

This rash was observed in 9.2 per cent of the 1941–51 series of initial attacks and in 13 per cent of the attacks utilized for therapeutic studies. For the entire group of 457 patients the incidence was 11 per cent (Table I).

Erythema marginatum is an evanescent, pink or faintly red, circinate, non-itching rash, which occurs on various parts of the body but practically never on the face. The colored margins are usually thin and the clear centers relatively large. The lesions, which are quite variable in size, are usually macular but, when extensive, they may be slightly papular. In spite of these typical characteristics, the rash can be confused with a somewhat similar appearing rash that is sometimes associated with childhood rheumatoid arthritis (Still's disease) and with other "toxic" rashes described in textbooks of dermatology, and, therefore, this manifestation cannot be accepted as being specific for rheumatic fever. Nevertheless, erythema marginatum is an important confirmatory sign, which, when present, may be quite helpful in making a diagnosis of rheumatic fever.

Erythema marginatum also has some prognostic significance although not to the same extent as subcutaneous nodules. Thus the incidence of significant murmurs indicative of valvular involvement was 69 per cent in patients with erythema marginatum (Table II) in contrast to a corresponding figure of 53 per cent for the entire series of 457 patients (Table I).

Prolongation of the P-R interval occurred in 33 per cent of all patients with erythema marginatum and in 30 per cent of those who had both this rash and significant murmurs (Table VI). These figures appear to be slightly greater than those for the incidence of a prolonged P-R interval in the entire group of initial attacks (25 per cent) and in all patients with significant murmurs (26 per cent).

Pericarditis also was somewhat more common in 33 patients who had both significant murmurs and erythema marginatum than in the entire group of 240 patients with significant murmurs (Table III), but congestive heart failure occurred no more often in heart patients with erythema marginatum than in the entire group of 240 heart patients (Table IV).

Correlation of Erythema Marginatum and Subcutaneous Nodules: That heart damage tends to be correlated to a high degree with subcutaneous nodules and to a moderate degree with erythema marginatum has already been indicated. Erythema marginatum and subcutaneous nodules also tend to be correlated with each other.

From data shown in Table VII it is evident that the incidence of erythema marginatum was 26 per cent in all patients with nodules in contrast to an incidence of 11 per cent in the total group of 457 patients, while the incidence of

TABLE VII

Influence of Subcutaneous Nodules on the Incidence of Erythema Marginatum

	Total cases	With erythema marginatum	
		Cases	%
All patients with initial rheumatic fever	457	48	11
All patients with subcutaneous nodules	54	14	26
All patients with significant murmurs	240	33	14
Patients with both subcutaneous nodules and significant murmurs	49	14	29

erythema in patients with both nodules and significant murmurs was 29 per cent in contrast to an incidence of 14 per cent in all patients with significant murmurs. Similarly, data in Table VIII show that the incidence of subcutaneous

TABLE VIII

Influence of Erythema Marginatum on the Incidence of Subcutaneous Nodules

	Total cases	With subcutaneous nodules	
		Cases	%
All patients with initial rheumatic fever	457	54	12
All patients with erythema marginatum	48	14	29
All patients with significant murmurs	240	49	20
Patients with both erythema marginatum and significant murmurs	33	14	42

nodules in all patients with erythema marginatum was 29 per cent in contrast to an incidence of 12 per cent for the total group of 457 patients while the incidence of nodules in patients with both erythema marginatum and significant murmurs was 42 per cent in contrast to an incidence of 20 per cent for all patients with significant murmurs.

Thus the incidence of erythema marginatum was about doubled in the presence of subcutaneous nodules and, conversely, the incidence of nodules was about doubled in the presence of erythema marginatum.

CHOREA

In the analyses used for compiling the data shown in Tables I and II, patients with chorea were included only if this manifestation was associated with significant murmurs or other stigmata of rheumatic fever; patients with so-called pure chorea were excluded. The incidence of chorea, when the data were so analyzed, was 14 per cent in the patients with initial attacks of rheumatic fever observed between 1941 and 1951, 11 per cent in the patients included in the therapeutic studies, and 13 per cent for the combined group of 457 patients.

Since the presence of heart disease tended to result in the inclusion of cases of chorea whereas the absence of cardiac involvement tended to cause exclusion of such cases from the analyses, the figure of 66 per cent shown in Table II for the incidence of significant murmurs in chorea is obviously heavily weighted.

In order to obtain a more exact picture of chorea in regard to its frequency and its association with signs of heart involvement, it is necessary to analyze all cases of chorea without selection. Such an analysis is not possible for the group of cases utilized for the therapeutic studies because this is a selected group, and patients with pure chorea often were not considered suitable for evaluation of the methods of treatment under investigation. However, it is possible to make an analysis of all cases of chorea (without selection) for the period from 1941 to 1951.

During this period, in addition to the 44 patients with chorea listed in Table I, 33 other patients in their initial attack of pure chorea were admitted to the wards of the hospital. From the data for the entire group of 77 chorea cases, presented in Table IX, the true incidence of chorea in patients in their initial attack of

TABLE IX

Incidence of Chorea in Initial Attacks of Rheumatic Fever and Incidence of Significant Murmurs in Patients with Chorea. Data for Period 1941–51

	Total cases	With chorea		With chorea and significant murmurs	
		Cases	% of total	Cases	% of chorea cases
Cases listed in Table I for period 1941–51	304	44		26	
Additional cases of pure chorea	33	33		0	
Total	337	77	23	26	34

rheumatic fever was 23 per cent and the incidence of significant murmurs in all patients with chorea was only 34 per cent.

Pertinent to this finding of a relatively low incidence of heart involvement in chorea, is our experience that when chorea occurs in patients with other stigmata of rheumatic fever, the involuntary movements usually do not develop until after the more acute signs of illness have subsided and sometimes even not until after the sedimentation rate has reached normal or near normal figures.

The foregoing observations are consistent with the view that chorea is generally a manifestation of mild rheumatic fever and/or that chorea only occurs when rheumatic fever is at a low level of activity. Although chorea is one of the least serious manifestations of rheumatic fever, it is at the same time one of the most specific, since typical choreiform movements are rarely caused by any condition other than rheumatic fever.

FEVER AND ELEVATION OF THE ERYTHROCYTE SEDIMENTATION RATE

Fever was observed in 86 to 90 per cent of the cases listed in Table I and elevation of the sedimentation rate in 90 to 97 per cent of cases. In the combined group of 457 initial attacks one or the other or both of these manifestations were noted in 97 per cent. The relatively few instances in which these two signs of inflammation or tissue destruction were not recorded were for the most part in patients who were not admitted to the House of the Good Samaritan until a number of weeks after the onset of rheumatic fever and in whom adequate observations had not been made during the early part of their illness.

These findings are consistent with our general experience that, except in cases of pure chorea, it is uncommon for at least some degree of fever not to be present at the onset of rheumatic fever and, particularly, for the sedimentation rate not to be definitely elevated during the early weeks of the disease. As a rule, elevation of the sedimentation rate continues considerably longer than does fever. In evaluating the sedimentation rate, it is important to remember that the development of congestive heart failure may slow the sedimentation rate and even cause an elevated rate to become reduced to within normal limits.

Although fever and elevation of the sedimentation rate are nonspecific manifestations that accompany many disease processes, they have considerable diagnostic importance. The presence of either or both of these signs is confirmatory of rheumatic fever but does not prove the diagnosis; whereas their absence, especially absence of an elevated sedimentation rate, strongly weights the evidence against active rheumatic fever.

ANTISTREPTOLYSIN-O TITER

Because of the relationship of rheumatic fever to antecedent beta hemolytic streptococcal respiratory infection the antistreptolysin-O titer is usually elevated in rheumatic fever. In the initial attacks of rheumatic fever shown in Table I titers of 400 units or more were recorded in 81 to 84 per cent.

These figures are consistent with those of a previously reported special study of the antistreptolysin-O titer,[3] in which we observed titers of 400 units or more in from 83 to 90 per cent of rheumatic fever patients with joint pain whose illness was of no more than four months' duration. This special study also indicated that in authentic cases of rheumatic fever, in which the diagnosis was documented by the development of typical signs of rheumatic heart disease, titers of 125 units or less occurred in only 0.9 to 1.5 per cent of cases.

The foregoing findings have led to the following conclusions regarding the *diagnostic significance* of the antistreptolysin-O titer:

(1) A titer of 400 units or more constitutes important confirmatory evidence of rheumatic fever but does not prove the diagnosis since such high titers sometimes can be due to antecedent streptococcal infection uncomplicated by any disease or complicated by some condition other than rheumatic fever.

(2) A titer of 125 units or less weights the evidence very strongly against rheumatic fever—especially in illnesses that are not of more than four months' duration.

(3) Titers of 159 to 317 units are in a borderline range and, in regard to the diagnosis of

rheumatic fever, have a borderline significance.

The antistreptolysin-O titer, although of considerable diagnostic importance, does not appear to have any significance in regard to *immediate prognosis*. Thus, if the 457 initial attacks recorded in Table I are divided into those with significant murmurs during observation at the House of the Good Samaritan (240 cases) and those without significant murmurs (217 cases), the incidence of titers of 400 units or more is found to be 82.1 per cent for the cases with heart disease and 82.5 per cent for those without heart disease. Similarly, in the previously published study to which reference has been made[8] the distribution of the antistreptolysin-O titer in cases of rheumatic fever and joint pain with carditis was found to be almost identical with that in cases without carditis (Fig. 1).

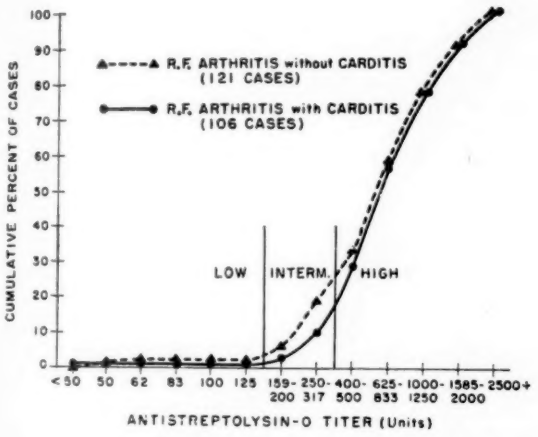
R.F. ARTHRITIS without CARDITIS (121 CASES)
R.F. ARTHRITIS with CARDITIS (106 CASES)
CUMULATIVE PERCENT OF CASES
LOW
INTERM.
HIGH
<50 50 62 83 100 125 159-200 250-317 400-500 625-833 1000-1250 1585-2000 2500+
ANTISTREPTOLYSIN-O TITER (Units)

Fig. 1. Distribution of antistreptolysin-O titers in rheumatic fever with and without carditis.

JOINT PAIN

This symptom, which is the last of the important manifestations of rheumatic fever to be discussed, occurred in 90 per cent of the 457 initial attacks listed in Table I.

In the vast majority of patients with joint pain two or more joints were affected, there were definite objective findings pointing to involvement of the joints, and the joint symptoms began at the very onset of the rheumatic fever attack. Furthermore, nearly all of the patients with joint pain due to rheumatic fever had fever and/or elevation of the sedimentation rate, and in close to 85 per cent of the cases the antistreptolysin-O titer was definitely elevated (400 units or more).

The foregoing facts provide evidence that an early diagnosis of rheumatic fever often is dependent upon recognition of a syndrome consisting of joint pain, fever and/or elevation of the sedimentation rate, and elevation of the antistreptolysin-O titer. In the present study this syndrome occurred in 74 per cent of cases (Table I).

Although the syndrome by itself cannot be accepted as being absolutely specific for rheumatic fever, it probably is caused by rheumatic fever far more often than by any other disease. Furthermore, in regard to the practical problem of management, it is important to keep in mind that a large number of patients presenting this syndrome at the onset of illness will develop murmurs indicative of valvular involvement before the illness has subsided. In the present study the incidence of such murmurs in patients with this syndrome was 50 per cent (Table II).

MORTALITY

Among the 304 patients who were observed between 1941 and 1951 there were five deaths. All five patients who died presented obvious signs of rheumatic valvular involvement with significant murmurs, and all developed congestive heart failure prior to death. Thus the incidence of a fatal outcome was 1.6 per cent for the entire group of 304 patients, 3.2 per cent for the 156 patients with significant murmurs, and 24 per cent for the 21 patients with congestive heart failure.

Pericarditis was present in three of the fatal cases, prolongation of the P-R interval in three cases, nodules in two cases, and erythema marginatum in one case.

The relatively low mortality rate (1.6 per cent) in this series of initial attacks is consistent with the concept that most deaths from rheumatic fever are due either to recurrences of the disease with consequent increase in severity of carditis or to the late effects of mechanically inefficient valves on the myocardium.

Clinical Course of Rheumatic Fever

Relation of Development of Significant Murmurs to the Duration of Illness: In order to study the question of when murmurs develop in the course of rheumatic fever, we have utilized the group of 304 patients with initial attacks observed between 1941 and 1951 since antirheumatic therapy, which conceivably might influence the picture, was not given to these patients or was given only in small doses or only for short periods. From this group a further selection has been made of 206 patients who were examined in a hospital within the first week of their illness. Information regarding this selected group is presented in Table X.

TABLE X

Incidence of Development of Significant Murmurs at Various Intervals after the Onset of 206 Initial Attacks of Rheumatic Fever. Data for Patients Observed between 1941 and 1951

Duration of illness (days)	Patients developing murmurs during interval		
	Number	Per cent of patients with carditis	Per cent of total patients
1–7	78	76	38
8–14	7	6.8	3.4
15–28	4	3.9	1.9
29–42	3	2.9	1.4
43–91	4	3.9	1.9
More than 91	7	6.8	3.4
Total	103	100	50

The data in Table X show that 103 patients (50 per cent) developed significant murmurs indicative of cardiac involvement some time between the onset and end of their attack. Of those who developed evidence of heart damage, murmurs were already present in 78 patients (76 per cent) when the patients were first examined in a hospital during the first week of illness. In only 25 patients (24 per cent of those who showed signs of carditis) did significant murmurs appear subsequent to the end of the first week. Murmurs were detected in seven patients during the second week of illness, in seven patients between the beginning of the third and end of the sixth week, and in four patients between the beginning of the seventh and the end of the thirteenth week of illness. In seven patients the appearance of murmurs was delayed until some time between the beginning of the fourteenth week and the patients' discharge from the House of the Good Samaritan.

The data from Table X have been used also to calculate the risk of significant murmurs developing in patients who did not present murmurs when examined at various intervals after the onset of their initial attack of rheumatic fever. The results of this analysis, shown in Table XI, indicate that the risk of significant murmurs developing subsequent to the onset of rheumatic fever was 50 per cent. However, if murmurs were not present by the eighth day of illness, the risk of such murmurs appearing later in the attack was only 20 per cent. The risk decreased to 15 per cent on the 15th day, 12 per cent on the 29th day, 10 per cent on the 43rd day, and 6 per cent on the 92nd day.

TABLE XI

Risk of Murmurs Developing in Patients Not Showing Signs of Carditis When Examined at Various Intervals after the Onset of Rheumatic Fever

Day of illness	Number of patients without carditis	Patients subsequently developing significant murmurs	
		Number	%
Onset	206	103	50
8	128	25	20
15	121	18	15
29	117	14	12
43	114	11	10
92	110	7	6

Thus, the results of this study suggest that most murmurs which develop in an initial attack of rheumatic fever become apparent early and that the risk of murmurs developing later rapidly decreases after the first week of illness.

Duration of Initial Attacks of Rheumatic Fever: Among the 304 patients who received little or no antirheumatic therapy and who were observed

TABLE XII

Proportion of Patients With Active Rheumatic Fever at Increasing Intervals after Onset of 269 Initial Attacks. Data for Patients Observed between 1941 and 1951

Weeks elapsed since onset	With active rheumatic fever	
	Cases	%
0	269	100
6	200	74
9	119	44
12	59	22
15	30	11
18	15	6

between 1941 and 1951, there were 269 patients with adequate data to allow for a study of the duration of the rheumatic attack. The results of this study are shown in Table XII.

The data in Table XII indicate that all evidence of active rheumatic fever had subsided within 12 weeks in almost 80 per cent of cases and within 15 weeks in almost 90 per cent. Thus it would appear that most of the initial attacks were self-limited and the vast majority of them subsided spontaneously within a period of 12 to 15 weeks.

In evaluating the foregoing results, it is important to keep in mind that all patients with recrudescences of rheumatic fever were excluded from this study and also that in nearly all instances penicillin was used either in daily prophylactic doses or in therapeutic doses whenever beta hemolytic streptococci were cultured from the throat.* Therefore, the self-limited nature of rheumatic fever observed here reflects the course of the disease when the effects of intercurrent streptococcal infection are kept at a minimum.

Therapeutic Implications

It is not the purpose of this paper to discuss the relative therapeutic value of the adrenocortical steroids, salicylates, and other antirheumatic drugs. Nevertheless, the data that have been presented have therapeutic implications requiring brief consideration.

The findings that are pertinent to the problem of therapy are the following:

(1) Rheumatic fever, at least when beta hemolytic streptococci in the upper respiratory tract are eradicated or highly suppressed with penicillin, runs a self-limited course, subsiding in most instances within a period of twelve to fifteen weeks.

(2) In spite of this self-limited course, an appreciable proportion of patients (a little more than 50 per cent in the present series) develop signs of cardiac involvement.

(3) When heart involvement results from rheumatic fever, the signs usually appear very early in the course of the attack—within a week in 76 per cent and within two to four weeks in about 85 per cent of the present series of untreated cases.

Experience suggests that the heart damage which so often results from rheumatic fever is due to two processes: inflammation with tissue damage at the beginning and, as time goes on, repair of inflammation with fibrosis and consequent deformity of valves and permanent changes in the myocardium. Furthermore, it seems reasonable to believe that the need for repair and hence the development of permanent cardiac damage can be prevented or lessened if the inflammatory process in the heart can be suppressed early in the attack and can be kept suppressed for the duration of the rheumatic episode.

If this premise is correct, then the optimum antirheumatic drug would be one which, when given in reasonably safe dosage, can cause a maximum degree of suppression of the rheumatic inflammatory process in the heart and can be continued in suppressive dosage over a sufficiently long period to cover the duration of the average self-limited attack of rheumatic fever.

The use of this drug would seem to be particularly important in patients who have definite active rheumatic fever and signs of carditis and in patients without significant murmurs who are seen early in an acute attack of rheumatic fever. In patients first seen four weeks or more after the onset of rheumatic fever and who are found not to have significant murmurs, the risk of valvular involvement

* The use of penicillin in ward patients at the House of the Good Samaritan began in 1945.

developing later in the attack is relatively slight, and, therefore, for such patients the need of a potent antirheumatic drug would seem to be less urgent.

Summary and Conclusions

(1) The clinical picture of rheumatic fever has been studied in 490 patients under the age of 17 years observed during their initial attack of the disease.

(2) The principal manifestations of rheumatic fever in these patients have been analyzed to determine their frequency, diagnostic importance, and significance in regard to immediate prognosis.

(3) Chorea, including pure chorea, was observed in 23 per cent of the patients. The incidence of the other principal manifestations of rheumatic fever, when cases of pure chorea were excluded, was found to be as follows: significant murmurs, 53 per cent; pericarditis, 6.3 per cent; congestive heart failure, 7.9 per cent; prolongation of the P-R interval, 25 per cent; subcutaneous nodules, 12 per cent; erythema marginatum, 11 per cent; fever, 89 per cent; elevation of the erythrocyte sedimentation rate, 92 per cent; and elevation of the antistreptolysin-O titer, 82 per cent.

(4) For purposes of making a diagnosis, all of the principal manifestations may be useful at one time or other. Significant murmurs and chorea (when typical) come closest to being specific for rheumatic fever. Chorea may appear in a pure form or may be associated with significant murmurs and other stigmata of rheumatic fever. For the murmurs of rheumatic heart disease to be indicative of active rheumatic fever they must be accompanied by other manifestations of the disease.

Next in diagnostic significance as a manifestation of rheumatic fever is joint pain, especially when it occurs as part of the syndrome of joint pain, fever and/or elevation of the sedimentation rate, and elevation of the antistreptolysin-O titer. When associated with significant murmurs, this syndrome provides important confirmatory evidence of active rheumatic fever. In the absence of murmurs and other signs of carditis it is less specific but still of diagnostic importance. Since the syndrome usually appears at the immediate onset of rheumatic fever, it is particularly helpful in making an early diagnosis. The remaining manifestations, since they usually occur in association with significant murmurs, chorea, or joint pain, are generally of diagnostic importance as confirmatory signs.

(5) From the point of view of immediate prognosis, the manifestations of carditis are obviously the most significant since in the absence of heart involvement rheumatic fever is a relatively benign disease. Significant murmurs are the most common sign of carditis, whereas congestive failure and pericarditis are the most serious signs. It is of interest that prolongation of the P-R interval, though presumably indicative of changes in the myocardium, was observed in patients with significant murmurs and other signs of carditis hardly more often than in rheumatic fever patients whose hearts, except for the electrocardiographic findings, were apparently unaffected.

Subcutaneous nodules and erythema marginatum show a varying degree of association with significant murmurs and other signs of carditis. Therefore, both of these manifestations, but particularly nodules, have considerable significance in regard to immediate prognosis. Erythema marginatum and nodules tend to be associated with each other.

Chorea is a manifestation of relatively mild rheumatic fever. When all cases of chorea are included in the analyses, the incidence of significant murmurs among patients with this manifestation in the present study was found to be only 34 per cent in contrast to an incidence of 50 per cent or more for patients with other manifestations.

(6) When significant murmurs indicative of valvular involvement develop during acute rheumatic fever, they usually appear relatively early in the illness. In the present study 76 per cent of murmurs were observed within one week after onset of the attack and about 85 per cent within two to four weeks after onset.

(7) Initial attacks of rheumatic fever run a self-limited course. In the present study all signs of active rheumatic fever subsided within twelve weeks in almost 80 per cent of cases and within fifteen weeks in nearly 90 per cent.

(8) The clinical findings that have been ob-

served have important implications in regard to the therapy of rheumatic fever. These implications have been discussed briefly.

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Evaluation of Clinical and Laboratory Factors in Diagnosis of Acute Rheumatic Fever*

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THE ACCURACY of diagnosis of rheumatic fever depends on the keenness of perception, profundity of knowledge, breadth of experience, and wisdom of judgment of the attending physician. How can clinical and laboratory procedures be used to assist? The Jones criteria for the diagnosis of rheumatic fever, originally tabulated in 1944,[1] have been modified recently by a committee of the American Heart Association.[2] The criteria are to be used as guides only. They do not make or rule out the diagnosis. Cardiologists are familiar with these criteria; therefore, the present discussion is devoted to the caution that must be exercised in applying the suggested patterns to patients suffering with illnesses resembling rheumatic fever.

Table I demarcates the prerequisites for a positive diagnosis of rheumatic fever. In the absence of at least one of these four requirements, it is impossible to be positive of the presence of this disease. However, even when one or more of them are present, they, *per se*, do not establish the diagnosis. For example, a patient, with definite history of rheumatic fever in the past, and with clear cut rheumatic heart disease, with arthritis, fever and elevated sedimentation rate, may be suffering from acute specific arthritis rather than acute rheumatic fever.

EVALUATION OF CLINICAL MANIFESTATIONS

Requirements for suspicion of rheumatic fever (Table I) are not as rigid as those for positive diagnosis. The major manifestations (Table I) of active rheumatic fever are common in rheumatic fever but may occur individually in other conditions, or may be so indefinite as to offer little assistance in diagnosis. Cardiac enlargement may occur in other illnesses than acute rheumatic fever, such as sickle cell anemia and acute benign nonspecific pericarditis. Murmurs may appear to be significant in the presence of anemia. High fever and tachycardia in a thin-chested child may be associated with loud apical systolic murmurs which are exceedingly difficult to differentiate from organic valvular deformity. Some murmurs of congenital heart disease may be confused with rheumatic involvement. Neither pericarditis nor congestive heart failure is characteristic of, though either may occur during the course of, acute rheumatic fever.

Migrating polyarthritis is characteristic of acute rheumatic fever, but many patients do not present this picture. Instead they show single joint involvement, or absence of redness, heat and swelling, or multiple simultaneous joint inflammation. Penicillin reactions may cause great confusion in diagnosis, particularly in the early stages of illness, for this antibiotic will have been administered to the patient suffering from streptococcal sore throat 10 to 14 days previously, and now the patient may have arthritis and fever.

Chorea, when typical, may be considered characteristic of rheumatic disease, but minimal abnormal movements may defy clear

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TABLE I

Diagnosis of Rheumatic Fever

Requirements for positive diagnosis

1. Positive past history of rheumatic fever
2. Rheumatic heart disease
3. Two or more major manifestations
4. At least one major and two minor manifestations

Requirements permitting rheumatic fever to be suspected

1. One major and one minor manifestation
2. Two minor manifestations

Major manifestations of active rheumatic fever

1. Carditis—cardiac enlargement, significant cardiac murmurs, pericarditis, congestive failure
2. Migrating polyarthritis
3. Chorea
4. Subcutaneous nodules
5. Erythema marginatum

Minor manifestations of active rheumatic fever

Clinical
1. Fever
2. Arthralgia
3. Previous rheumatic fever
4. Rheumatic heart disease

Laboratory
1. P-R prolongation of ECG
2. Leucocytosis
3. Increased sedimentation rate
4. C-reactive protein present
5. Preceding infection with group A streptococcus
   (a) Bacteriologic proof
   (b) Antibody response (e.g., ASLO elevation)

definition, and the possibility of neurotic tics may simulate minor choreiform manifestations.

Subcutaneous nodules and erythema marginatum give evidence of acute rheumatic fever when they are characteristic. So often, however, only one or two nodes appear, or atypical skin lesions are seen, that the diagnosis of these lesions cannot be made accurately.

As for the minor clinical manifestations (Table I), fever and arthralgia may occur in such a wide variety of illnesses, that their lack of specificity permits these findings to be considered as consistencies after the diagnosis of rheumatic fever has been made. Again, the history of previous rheumatic fever and the presence of rheumatic heart disease offer little assistance in evaluating a current illness.

Evaluation of Laboratory Manifestations

The minor laboratory manifestations (Table I) (P-R prolongation, leucocytosis, increased sedimentation rate, and presence of C-reactive protein) also lack specificity and give evidence only of inflammation, but provide no help in determining the source of the inflammation. Recently, emphasis has been placed on the importance of a previous infection with group A beta hemolytic streptococcus, as an indication of rheumatic fever.[2] What constitutes a streptococcal infection, however, has not been agreed upon as yet. According to some investigators, the mere presence of this organism in the nose or throat signifies infection.[3] A more general view is that infection is present when beta hemolytic streptococci are recovered, and when there is immunologic response to

TABLE II

Isolation Rate of Group A Beta Hemolytic Streptococci per Month from the Throats of Children Six to Nine Years of Age

Year of study	Number of months of study	Range		
		Minimum	Maximum	Average
1953	4	2.5	8.7	5.1
1953–54	8	3.8	10.6	8.1
1954–1955	8	10.2	17.1	14.2
Special study	8	5.3	20.0	14.25

Number and per cent of children from whose throats group A beta hemolytic streptoccoci were recovered at least once

		Positive beta hemolytic streptococci	
		Number	%
1953	4	47	13.7
1953–1954	8	126	37.9
1954–1955	8	137	41.1

their presence, that such infection is *overt* if clinical symptoms also are present and *occult* in the absence of clinical findings.[4] In studies conducted in the laboratories of the National Children's Cardiac Hospital (Table II), we found group A beta hemolytic streptococci in the throats of approximately 14 per cent of children 6 to 9 years of age attending the public schools of Dade County, Florida, cultured once during the eight-month school year.[5–7] When the same children had their throats cultured monthly during the same period, group A streptococci were isolated from the throats of over 40 per cent of these children (Table II).

To determine whether these organisms were responsible for carrier states or whether they evoked an immunologic reaction, we did serial antistreptolysin-O titrations (Table III). A rise of two tubes or more in the titer was considered a response. Half the group A streptococci were associated with titer elevations; 5 per cent of children with no beta hemolytic streptococci also showed a rise, as did 18 per cent of those children from whose throats group C, F or G organisms were recovered.

TABLE III

Significant Antistreptolysin-O Titer Rise

Bacteriologic category	Total sera	<2 Tube rise	2 or > Tube rise	
			Number	%
No βHS or group B	101	96	5	5.0
Group C, F, G	39	32	7	17.9
Total nongroup A	140	128	12	8.6
A nontypable	43	23	20	46.5
A typable	24	10	14	58.3
Total group A	67	33	34	50.7

Relation of Positive Cultures and Incidence of Rheumatic Fever: These figures contrast sharply with our expectations of frequency of acute rheumatic infections, if predicated on the basis of 3 per cent of streptococcal infections progressing to rheumatic sequelae. That acute rheumatic episodes are uncommon in the Greater Miami area is confirmed by three additional studies. Check of rheumatic heart disease[8] in native-born Miami school children (Table IV) revealed three definite and two suspicious instances among 1,001 students. The second study[9] was a review of almost 3,000 consecutive autopsies, including 72 hearts showing rheumatic heart disease (Table IV). These 72 represent all who died of rheumatic disease as well as those hearts in which rheumatic lesions were discovered first at postmortem examination. Of the total number of autopsies, 25 per cent were in native Floridians, and 75 per cent in non-Floridians (Table IV). Rheumatic heart disease, however, occurred in only 8 per cent of the Floridians, one-

TABLE IV

Frequency of Rheumatic Heart Disease in Miami, Florida

Rheumatic heart disease in Miami school children (1950)

	Number examined	With R.H.D.	Suspicious
White	579	0	0
Negro	422	3	2
Total	1,001	5	
	Rate: 5 per 1,000		

Rheumatic heart disease found at autopsy in Miami, Florida (1950–55)

Deaths	6,258
Autopsies	2,967
Rheumatics	72 (2.5%)

Frequency of rheumatic heart disease observed in autopsies on Florida-born in contrast to those born elsewhere

	%	
	Florida-born	Outside Florida
Autopsy rate	25	75
Rheumatic heart disease	8	92

third of the anticipated frequency (Table IV). The third study was an intensive case registry of rheumatic fever in which all physicians and hospitals who might have seen rheumatic patients were contacted at monthly intervals for 13 months to October, 1956 for detailed reports on each rheumatic fever suspect. This case register brought to light only 17 acute episodes in 13 months (Table V).[10]

TABLE V

Frequency of Active Rheumatic Fever and Glomerulonephritis as Reported in a Special Case Register

Age	Rheumatic fever	Glomerulonephritis
Under 6	1	6
6–9	3	6
10–15	3	5
16–20	4	0
21+	6	1
Total	17	18

From these data, several conclusions are possible. The presence of group A beta hemolytic streptococci was not sufficient evidence of infection as far as its etiologic relationship to acute rheumatic fever is concerned. The same conclusion was valid when these organisms were associated with antistreptolysin-O responses, thus eliminating occult streptococcal infections as a hazard, in our studies. Possibly the response to streptococci must be of sufficient intensity to produce not only immunological but also clinical evidence of illness before the patient is jeopardized with rheumatic fever. However, our current investigations have failed to date to bear out this concept. Since all of our surveys have been carried out in a tropical climate, this environmental factor must be considered as a possible influence on the incidence and prevalence of rheumatic fever and heart disease. Review of published reports[7] indicates that there is a close parallelism between the latitude of the area studied, and the prevalence of rheumatic heart disease (Table VI). The range of rates is such that the highest southern report is one-third of the lowest northern. Whether or not the climatic factor does influence rheumatic prevalence is a

TABLE VI

Rheumatic Heart Disease Prevalence Northern vs. Southern Climates

Climate	Range rate/1,000
Northern	16.3 to 45.0
Southern	3.8 to 5.0

study[11] presently being planned, in which a number of investigators in various geographic locations have agreed to carry out an identical cooperative program.

One last point should be mentioned about the significance of the recovery of group A streptococci from throat cultures. The number of colonies has been mentioned. In our work to date, the number of colonies recovered shows consistent correlation neither with antistreptolysin titer level or rise, nor with illness sufficient to occasion school absence.

For completeness, additional suggestive signs and symptoms of acute rheumatic fever (Table VII), as promulgated by the modified Jones' criteria,[2] are those findings common to a wide variety of illnesses.

TABLE VII

Suggestive Signs and Symptoms of Rheumatic Fever

- A. Systemic
  - Loss of weight
  - Easy fatigability
  - Tachycardia during sleep
  - Malaise
  - Sweating
  - Pallor
  - Anemia
- B. Local
  - Epistaxis
  - Erythema nodosum
  - Precordial pain
  - Abdominal pain
  - Headache
  - Vomiting
- C. Family history of rheumatic fever

Trafuril Skin Test

Many investigators have sought more adequate laboratory aids to assist in the diagnosis of rheumatic activity. Such tests have been reported frequently but none has attained

widespread acceptance. One such procedure,[12,13] originated in the laboratory of the National Children's Cardiac Hospital, will be described because of its simplicity and high degree of accuracy. The tetrahydrofurfuryl ester of nicotinic acid (Fig. 1) is a rubefacient

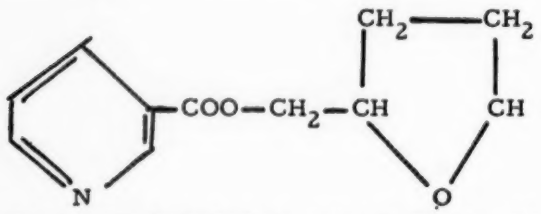

Fig. 1. Tetrahydrofurfuryl ester of nicotinic acid (Trafuril®, Ciba)

used in Europe for the treatment of muscular aches and pains. When an ointment containing this compound is rubbed into the skin of a normal person, a redness of the area occurs within 30 minutes, sometimes with mild spread beyond the contact region, and sometimes with mild edema. When applied topically to the skin of a patient showing rheumatic activity, the ointment fails to evoke the redness and even may cause blanching. In our experience, with rigid criteria for reading the reaction, 95 per cent of several hundred normal controls showed a typical red response, an additional 1.5 per cent were doubtful, and only 3.5 per cent were false and nontypical. Over 90 per cent of patients with congenital heart disease also displayed normal redness. Among patients considered to have definite but inactive rheumatic disease, over 97 per cent showed normal redness. Active rheumatic fever, on the other hand, was accompanied by nontypical blanching or absence of erythema in 86 per cent of the 114 patients tested. All these tests were run as "double blinds," and in the final analysis, a patient was considered to have active disease if the attending physician thought that he did.

This skin test has been checked in a number of other laboratories, but much more work will have to be done before it can be accepted finally. Other diseases, such as rheumatoid arthritis and streptococcal infections may cause nontypical responses. Such responses generally return to normal promptly in the case of streptococcal infections, while the abnormal reactions tend to persist as long as rheumatic activity lasts. Data on skin testing in rheumatoid arthritis[14–16] have been published but require clarification and confirmation.

Differential Diagnosis

The difficulties of interpretation of the manifestations of rheumatic fever have been emphasized. These problems in atypical episodes cause many conditions to be confused with rheumatic fever. In a review[17] of over 2,000 successive records of patients in the outpatient clinic of the National Children's Cardiac Hospital suspected of suffering from heart disease, 47 per cent had no heart disease or rheumatic fever, 23.5 per cent showed rheumatic and 23.5 per cent congenital involvement, and about 6 per cent (117 cases) had other illnesses which we were able to place in one of the following categories: blood disorders, such as sickle cell anemia, parasitic infestations, and allergic purpura; cardiac disorders, such as arrhythmias, diphtheritic myocarditis, and acute benign pericarditis; endocrine or nutritional disorders, including thyroid disturbance, calcium deficiency or rickets; febrile illnesses, exemplified by tuberculosis, cellulitis, dental caries, and many fevers of unknown origin; organic neurologic disease, such as epilepsy, brain tumor, and poliomyelitis; neuroses; renal involvement; respiratory conditions, e.g., tonsillitis, bronchitis, bronchiectasis, allergic rhinitis or asthma, and pulmonary tumor; and a few miscellaneous conditions such as cervical rib and ulcerative colitis with rheumatoid arthritis.

Summary

This presentation attempted to demonstrate the extreme care which must be exercised in the evaluation of any finding or group of findings as indication of the presence of active rheumatic fever. This caution must be exerted whether the signs and symptoms observed are major or minor manifestations, clinical or laboratory. No combination of findings makes the diagnosis. The diagnosis of acute rheumatic fever must be made by the attending physician.

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Prevention of Rheumatic Fever*

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THE CONCEPT that acute rheumatic fever follows infection with the group A streptococcus in approximately 3 per cent of cases is now generally accepted. The processes involved in the pathogenesis of the disease following streptococcal infection are not known, but the evidence in support of a relationship is overwhelming. This evidence stems from both clinical and laboratory observation. Many patients presenting with acute rheumatic fever give histories of preceding upper respiratory infection, and, if careful bacteriologic and serologic examination of these patients is carried out it is possible to show unequivocally in something approaching 100 per cent of instances that a preceding upper respiratory infection with the group A streptococcus did indeed occur.[1,2] A third line of evidence implicating the group A streptococcus in the etiology of rheumatic fever is derived from the fact that prophylactic treatment of known rheumatic patients with sulfonamides and with various penicillin preparations can tremendously reduce the incidence of rheumatic recurrences.[3–5]

The use of antibacterial drugs in the prophylaxis of rheumatic fever falls into two categories: (1) primary prevention, which means the abortion of the first attack of acute rheumatic fever through adequate early treatment of streptococcal infection and (2) secondary prevention, or prophylaxis of patients who are known to have had one or more attacks of acute rheumatic fever. There is now a wide background of experience on which to draw in setting up rheumatic fever prevention programs, although definitive information on the most efficacious means available to prevent both primary and secondary attacks still is not available. This is due in large part to the fact that new preparations are continually being introduced to medical practice and until further data are accumulated about methods of administration, dosage, and properties of the drugs, all recommendations must be tentative.

This situation is recognized by the Committee on Prevention of Rheumatic Fever of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association which from time to time issues revised statements of recommendation for rheumatic fever prophylaxis. In addition to making periodic recommendations in the light of the latest available information, this Committee also has established certain general procedures to be followed in carrying out prophylaxis. These principles are as follows: (1) Prophylaxis should be given to all patients who have a well documented history of rheumatic fever or chorea or who show definite evidence of rheumatic heart disease. (2) In order to be effective, prophylaxis must be *continuous* throughout the year, and should not be directed only at overt respiratory infections. (3) Prophylaxis should begin with the diagnosis of rheumatic fever, after therapy with a course of penicillin adequate to eradicate the group A streptococci from the pharynx. (4) The duration of prophylaxis has not been determined, and indefinite continuation is currently recommended.

The current recommendations of the American Heart Association for the prevention of rheumatic fever are shown in Table I.[6]

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TABLE I

Procedures Currently Recommended by The American Heart Association for Prevention of Rheumatic Fever

(1). Treatment of streptococcal infections in the general population
Intramuscular penicillin
Benzathine penicillin G
Children—600,000 to 900,000 U IM (one injection)
Adults—900,000 to 1,200,000 U IM (one injection)
or
Procaine penicillin with aluminum monostearate in oil
Children—300,000 U IM q 3rd day x 3 injections
Adults—600,000 U IM q 3rd day x 3 injections
Oral penicillin
Children and Adults—200,000 to 250,000 U t.i.d. for 10 days
Broad spectrum antibiotics
Useful when patient is sensitive to penicillin. Full therapeutic dosage for full 10 days
Not recommended
Penicillin troches or lozenges and sulfonamides are not effective in eradicating streptococcal infections
(2). Prevention of streptococcal infections in rheumatic individuals
Intramuscular
Benzathine penicillin G—1,200,000 U IM once a month
Oral
Sulfadiazine—0.5 to 1.0 g once a day throughout the year (the smaller dosage for children under 60 lb)
or
Penicillin—200,000 to 250,000 U once or, preferably, twice a day

The most comprehensive and detailed analysis of the general principles of prophylaxis currently available is contained in the second report of the Expert Committee on Rheumatic Diseases of the World Health Organization.[7] This group in its report considered primary prevention in considerably more detail than has been done previously.

The major activities being carried on in the field of rheumatic fever prophylaxis today are concerned with evaluations of the currently available prophylactic agents, primarily the sulfonamides and various preparations of penicillin. However, these pharmacologic methods of prophylaxis contain certain inherent disadvantages. The best known of these are the toxic reactions to the sulfonamides, the most serious of which are agranulocytosis, and the sensitivity reactions to penicillin preparations. There is no solid information available as to whether or not antimicrobial drug prophylaxis alters the patient's native immunologic mechanisms. It is conceivable that such an alteration may be the most severe hazard of chemoprophylaxis. Denny, Perry and Wannamaker[8] have recently shown that adequate penicillin treatment of patients with streptococcal upper respiratory infections inhibits the formation of type-specific streptococcal antibody. It is highly probable that continuous chemoprophylaxis also inhibits natural immunity by preventing prolonged residence of group A streptococci in the upper respiratory tract. For these reasons a more biologic method of preventing streptococcal infections and rheumatic fever would be most valuable. An approach to such a method might be provided by a vaccine effective against the many known types of group A streptococci. A vaccine which would render active immunization possible could conceivably provide permanent protection against streptococcal infections. Since there are many known serological types of group A streptococci and since immunity to group A streptococci appears to be type specific, any such vaccine which might be developed in the distant future would have to be a so-called polyvalent vaccine, one that would protect against infection with any of the great number of known Lancefield types.

Past Experience

The three agents which have been most widely used and extensively studied in the prophylaxis of rheumatic patients are the sulfonamides, most commonly sulfadiazine, oral penicillin, and intramuscular benzathine penicillin G. A comparison of the advantages and disadvantages of these preparations in use for continuous prophylaxis against group A streptococcal infections is shown in Table II.[9]

Before discussing the results obtained by var-

TABLE II*

Methods of Continuous Chemoprophylaxis

Antibiotics	Advantages	Disadvantages	Recommended dose	Toxicity
Sulfadiazine	1. Easily administered 2. Well absorbed 3. Inexpensive 4. Established effectiveness	1. Frequent breaks in routine 2. Risk of serious toxicity 3. Resistant streptococci 4. Bacteriostatic	1.0 g/day	Skin eruptions 0.5% Blood reactions 0.01%
Oral penicillin	1. Bactericidal 2. Serious toxicity rare 3. No resistant streptococci	1. Frequent breaks in routine 2. Irregular absorption 3. Costly 4. Minimum effective dose not well established	200,000–250,000 units once or twice daily	Urticaria; angioneurosis "serum type sickness" 0.3–0.7% Anaphylaxis "Periarteritis" rare
Repository benzathine penicillin	1. "Break" in prophylaxis less likely 2. Single dose usually eliminates carrier state 3. Economical 4. Close patient contact 5. Other advantages of penicillin (see oral penicillin)	1. Requires injection 2. Moderate local soreness	1,200,000 units I.M. once monthly	Urticaria Angioneurosis 1.2% "Serum type sickness" Anaphylaxis "Periarteritis" ?

* This table is reproduced with the permission of Dr. Gene H. Stollerman from *Am. J. Med.* 17: 757, 1954.

ious groups which have used these prophylactic agents, certain general comments are in order. Oral sulfadiazine and oral penicillin have in common the inherent disadvantage of dependence on reliable patient cooperation. Without faithful cooperation from the patient, effective prophylaxis cannot be maintained with either of these oral agents, and even in the most carefully controlled study of prophylaxis it is not possible to determine whether streptococcal infections and occasional recurrences of rheumatic fever are due to genuine streptococcal "break throughs" or to failure in patient cooperation. When benzathine penicillin G is administered by intramuscular injection every four weeks there is no doubt that the prophylactic program is maintained. However, from the practical point of view, parenteral administration demands a monthly visit to a physician or a clinic, and in many instances such close patient contact is impossible.

SULFONAMIDE PROPHYLAXIS

It has been known for almost 20 years that the incidence of rheumatic recurrences can be greatly reduced by sulfonamide prophylaxis. Since the time of the first reports of Coburn and Moore[10] and of Thomas and France[11] many studies of sulfonamide prophylaxis of rheumatic patients have been reported; in the majority of them sulfadiazine has been employed although the results probably would be comparable with any other sulfonamide preparation. The combined experience of many studies gives evidence that sulfonamide prophylaxis can reduce the incidence of rheumatic recurrences by at least 85 per cent.[12] With careful supervision of the administration of oral sulfonamides the incidence

of rheumatic recurrences might be even less than 15 per cent. The sulfonamides, unlike penicillin, are bacteriostatic and not bactericidal. For this reason the sulfonamides should not be used in the prophylaxis of the rheumatic patient until the streptococcal carrier state, if it exists, has been eliminated by a therapeutic course of a bactericidal antibiotic, preferably penicillin. Since the sulfonamides cannot eliminate the carrier state they are not effective drugs to use for prophylaxis under epidemic conditions. Some strains of sulfonamide resistant streptococci appeared during large scale prophylaxis programs conducted by the Armed Forces during World War II. The development of such resistant strains of streptococci does not constitute a major threat in the prophylaxis of patients in the civilian population. Of much more importance in sulfonamide prophylaxis of rheumatic children are the possible severe toxic reactions, particularly agranulocytosis and exfoliative dermatitis. Frequent white blood cell counts should be carried out on patients during the first few weeks of sulfonamide prophylaxis.

ORAL PENICILLIN PROPHYLAXIS

Few well controlled studies from the civilian population in which penicillin has been administered orally in daily small doses to rheumatic patients have been reported. The studies that have been reported to date indicate that penicillin is at least as effective as the sulfonamides in preventing recurrences of rheumatic fever, and it is still the prophylactic method of choice of the majority of clinics and physicians.[13] Although oral penicillin is more expensive than sulfadiazine it has the advantage of being bactericidal and of having caused the development of no drug resistant strains of group A streptococci to date. Oral penicillin carries with it the disadvantage of irregular absorption from the gastrointestinal tract.

Much of our most valuable information on oral penicillin prophylaxis of both adult rheumatic subjects and of normal adults has been obtained from the carefully controlled studies carried out at the Francis E. Warren Air Force Base under the direction of Charles H. Rammelkamp, Jr.[14,15] It is still not known whether the data obtained from the Fort Warren studies are applicable to outpatient pediatric rheumatic groups.

A small percentage of patients on oral penicillin prophylaxis develop hypersensitivity reactions during the course of their prophylactic treatment. The exact incidence of sensitivity reactions is difficult to determine because of the lack of controlled observations made in the framework of definite criteria. However, the best available indications are that the incidence of sensitivity reactions from the administration of small daily prophylactic doses of penicillin lies in the range of 1 per cent.

REPOSITORY PENICILLIN (INJECTABLE BENZATHINE PENICILLIN G) PROPHYLAXIS

Benzathine penicillin G as a prophylactic agent in rheumatic patients has now been in use for eight years and a considerable amount of information has been accumulated. It has the advantage common to all penicillin preparations of being bactericidal; in addition, the monthly administration of 1.2 million units of benzathine penicillin G constitutes what is generally considered to be an eradicating dose of penicillin for group A streptococci. Also, a detectable penicillin blood level persists for at least three weeks following each injection of 1.2 million units of the preparation. The factor of forgetfulness on the part of the patient is eliminated completely by the use of repository penicillin as the preparation is injected by a physician or nurse.

The number of recurrences of rheumatic fever observed in groups of patients on benzathine penicillin G has been consistently less than the number reported in studies of patients on the two oral methods of prophylaxis. Stollerman *et al.* in a study of 125 rheumatic patients maintained on 1.2 million units of benzathine penicillin G monthly for a period of two years observed no recurrences of acute rheumatic fever and evidence of streptococcal infection in only three patients.[16] Other groups have noted a similar absence of rheumatic recurrences or at least a very low incidence.[17,18]

The Irvington House Prophylaxis Study

In an attempt to obtain definitive information on the relative efficacy of three methods of

prophylaxis against rheumatic fever, Irvington House on May 1, 1954 began a statistically controlled five-year study of 407 patients with unequivocal histories of rheumatic fever.[18] By a method of random selection devised to give maximum comparability of groups in terms of age, sex, number of attacks of rheumatic fever and period of time elapsed since the last previous attack the patients were assigned to one of three prophylactic programs. The three regimens under study are: (1) Sulfadiazine one gram a day by mouth in a single dose. (2) Buffered potassium penicillin G 200,000 units a day by mouth in a single dose one-half hour before breakfast. (3) Benzathine penicillin G 1.2 million units in 2 cc by monthly intramuscular injection.

Each patient is seen in a clinic session monthly at which time in addition to a history taken every month and a physical examination every other month, throat cultures are taken on each clinic visit and blood for streptococcal antibody determinations is obtained on every other clinic visit. Streptococcal infections are detected as follows: throat cultures are taken on every patient at each monthly clinic visit and all beta-hemolytic streptococci are grouped with an antiserum to the group A streptococcus.[19] Antistreptolysin-O determinations are done on each bleeding from every patient.[20] These bleedings are taken bimonthly and whenever an elevation is found in the routine antistreptolysin-O, a serial determination of antistreptolysin-O, of antistreptokinase, and of antihyaluronidase is carried out on several successive monthly bleedings from the patient.[21,22]

Streptococcal Infections: At the end of the third year of this study the data have been obtained from 890 patient years of experience, the years being distributed equally among the three prophylaxis groups. A total of 145 streptococcal infections have been detected in the 407 patients in the study group over the three-year period. The distribution of these infections by prophylaxis groups was: benzathine penicillin G, 21; sulfadiazine, 67; penicillin, 57. The difference in the number of streptococcal infections between either of the oral groups and the bicillin group was statistically significant, whereas the difference in the number of infections in the two oral groups was not significant. The number of infections followed by recurrences of acute rheumatic fever and the percentage of the total infections for each prophylaxis group which this number represents are shown in Table III.

TABLE III

Irvington House Prophylaxis Study
Percentage of Streptococcal Infections Followed by Rheumatic Recurrences (Three-Year Experience)

	Oral penicillin	Sulfadiazine	Benzathine penicillin G (parenteral)
Number of streptococcal infections	57	67	21
Number of infections followed by rheumatic recurrences	12	6	1
Percentage	21	9	5

From these data it appears probable that injectable benzathine penicillin G given every four weeks as in this study is a more effective method of preventing streptococcal infections and recurrences of rheumatic fever than are either of the two oral regimens being studied. Some of this superiority probably is more apparent than real, however, since the administration of the injectable preparation is carried out at the clinic sessions whereas there is no external supervision of the patients taking oral prophylaxis.

Recurrence Rate: Several unforeseen findings are developing in the course of this study. One of these is more recurrences of acute rheumatic fever in the group of patients receiving oral penicillin than in the group receiving oral sulfadiazine. There still have not been enough recurrences of acute rheumatic fever to give statistical significance to this difference, but if the present trend persists and the recurrence rate continues at its present level to the end of

the five-year period this difference may have statistical as well as practical significance. It is worthy of note that the present recommendation of the Committee on Rheumatic Fever and Congenital Heart Disease of the American Heart Association is 250,000 units of penicillin by mouth twice a day rather than 200,000 units once a day, the amount being taken by patients in the oral penicillin group in this study.

Age Incidence of Streptococcal Infection: Another unexpected finding at the end of the first two years of this study is that when the streptococcal infections noted in the groups of children on oral prophylaxis are charted by age, the incidence in the younger age group (children six to ten years of age) is significantly higher than in the children in the same age group receiving the injectable penicillin preparation. This observation is of particular interest since it is in this age group that the highest incidence of streptococcal infections occurs in the general population. In known rheumatic children the risk of streptococcal infections and recurrences of acute rheumatic fever is highest in the first few years following the first attack of acute rheumatic fever.[9]

The distribution of the streptococcal infections by age in the three prophylaxis groups for the two-year period, representing a total of 574 patient years of experience, is shown in Figure 1. The numerical data from which the figure was made are presented in Table IV, where the number of streptococcal infections for each age group plus the percentage of patient years which these infections represent are tabulated. The differences in the age groups are statistically significant.

For the total group regardless of prophylaxis the proportion of streptococcal infections declines significantly with age. When the total

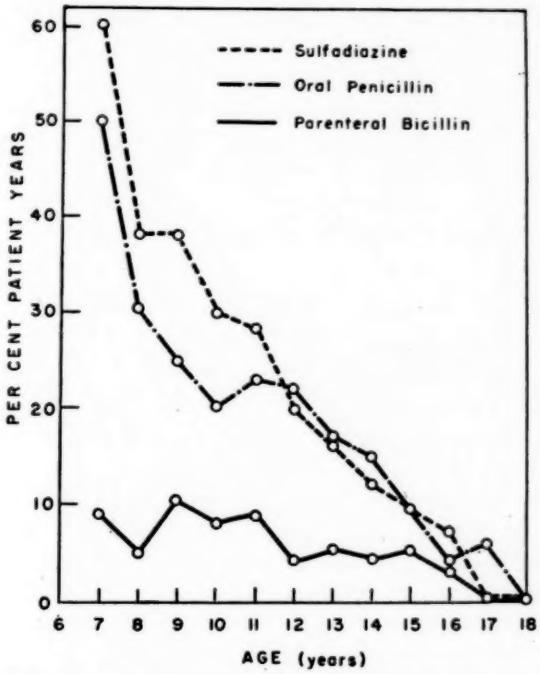

Fig. 1. Distribution of streptococcal infections by prophylaxis groups and age. (From data of first two years of Irvington House Prophylaxis Study.)

TABLE IV

Irvington House Prophylaxis Study
Prevalence of Streptococcal Infections by Prophylaxis and Age

Age	Bicillin			Penicillin			Sulfa			All drugs		
	Number infections	Patient years	%	Number infections	Patient years	%	Number infections	Patient years	%	Number infections	Patient years	%
6–10	6	58.3	10	15	53.3	28	24	56.0	43	45	167.6	27
11–15	6	115.2	5	22	119.4	18	22	123.8	18	50	358.4	14
16 and over	0	16.8	0	1	18.5	5	0	12.7	0	1	48.0	2

group is separated into different prophylaxis groups, in both of the oral groups the decline with age is significant; in the parenteral benzathine penicillin group, although the prevalence does decline, the figures of incidence are too small to warrant a definitive statement at the present time.

The current indications are that at the end of the five-year period projected for this study it will be possible to make definitive comparison of the effectiveness of the three prophylactic regimens being studied in relation both to incidence of streptococcal infection and recurrences of rheumatic fever. In addition, the natural history of rheumatic heart disease in the face of well maintained prophylaxis is being studied in this large group of patients.

Summary

The incidence both of first attacks of rheumatic fever and of recurrences of the disease in patients who have had one or more attacks can be greatly reduced. Early adequate treatment of streptococcal infections definitely can reduce the incidence of rheumatic fever. When rheumatic fever does occur, following the eradication of the group A streptococcus by an adequate course of penicillin therapy, recurrent attacks can be prevented in most instances by the continuous administration of any one of several antibacterial drugs. It is to be hoped that ultimately a more biologic method of preventing streptococcal infections and acute rheumatic fever will be available. However, until this does occur, the current available methods of treating and preventing streptococcal infection can greatly reduce the incidence of rheumatic fever and of recurrences of the disease.

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Complications of Rheumatic Fever*

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IN THE 17th century, Boerhaav made the observation: "Rheumatic fever sometimes invades the brain, the lungs, and the bowels as well as the joints." Nearly 150 years later, Laségue, in his treatise on rheumatism, made the same observation and is credited with the much quoted statement: "Rheumatic fever licks the joints, pleura and meninges, and bites the heart." Not infrequently, we, as physicians, forget the basic concept of disease and find ourselves interested in only a part of the whole. Particularly is this true in this day of specialization. It is the purpose of this discussion to once again bring to our attention the protean manifestations of this disease entity, rheumatic fever. It is only when the invasion of a tissue or an organ is of such magnitude as to produce symptoms that we are able to make a diagnosis. The subclinical and associated picture is frequently overlooked only to manifest itself in later years.

CENTRAL NERVOUS SYSTEM

Meningoencephalitis: Occasionally the acute attack of rheumatic fever does more than "lick the meninges." The invasion of the central nervous system is so explosive as to produce signs and symptoms of severe meningeal irritation and as a consequence, the term "encephalitis rheumatica" (meningoencephalitis) has been suggested as an identifying name for these manifestations of the disease. Rarely does a patient expire from Sydenham's chorea; however, in those few cases that have come to autopsy, the findings have been described as a diffuse meningoencephalitis. On microscopic examination, the lesions are usually rather widespread and for the most part limited to an engorgement of the blood vessels, with numerous thromboses in the small arteries and veins. This, in turn, results in proliferation and fatty infiltration of the endothelium with the end result being a degree of softening with exudation and round cell infiltration around the small vessels. Associated changes are found in the glia, nerve cells, and in the pia-arachnoid. Although the spinal fluid is reported to be sterile, and its chemical components within normal range, one may find nevertheless enough cells in the spinal fluid to make a diagnosis of aseptic meningitis. On occasion, the initial symptoms are so classical of meningeal irritation that the admitting diagnosis is, "possible meningitis." Because of the paucity of material, there has been no unanimity of opinion as to the classic pathologic picture other than that commonly associated with the general term meningoencephalitis.[1]

Hyperpyrexia, with temperatures as high as 110° F and resultant cerebral damage, is another example of rheumatic fever invading "sometimes the brain." This was such a common manifestation of the disease that in England in the latter part of the 18th century, a special committee was appointed to investigate this phenomenon. It was concluded that hyperpyrexia was most common in the first attacks of rheumatic fever where it might suddenly supervene in apparently favorable cases and half the patients would die. This occurred before the advent of salicylates and since that time, hyperpyrexia has been documented rarely. In a case reported in 1951, by Cruickshank,[2] a 20-year-old male in his first attack of acute rheumatic fever developed hyperpyrexia during the early stages of his hospitalization. At the height of the

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febrile episode, he developed generalized clonic convulsions which gradually changed to intermittent tonic type seizures associated with arching of the back. Between spasms he became deeply comatose with widely dilated, fixed pupils, flaccid limbs and absent reflexes. This patient remained comatose for approximately 24 hours, then began to regain his sensorium. After completely recovering from the acute attack of rheumatic fever, he continued to have a speech hesitancy.

Psychotic Complications: Whitman *et al.*[3] reported rheumatic brain disease with psychiatric manifestations as a sequel to acute attacks of rheumatic fever and as an etiologic factor in convulsions. Only through the history were they and others able to correlate the rheumatic infection with the psychiatric manifestations. Electroencephalography was of no specific diagnostic value. Those psychiatric patients who were known to have or to have had rheumatic fever required very close observation for the manifestations of rheumatic recurrence, since a recurrence or a reactivation prolonged the psychiatric disorder. The psychotic manifestations of a patient with rheumatic brain disease may resemble any psychosis. Bruetsch[4] felt that the involvement of the brain in a young individual resembled a picture of dementia praecox while rheumatic infection involving the brain in more advanced life resulted in psychiatric syndromes such as involutional, senile psychoses or even severe depressions. It was his feeling that behavior disorders in children following chorea were not uncommon sequelae and were the result of persistence of the rheumatic infection.

Respiratory System

The incidence of rheumatic pleural effusion and pneumonitis is reported to vary from three to fourteen per cent. Although it may be found very early in the rheumatic episode, it is more often associated with acute pancarditis. The physical signs are fleeting and because the patient appears much sicker than physical examination reveals, the diagnosis is usually made by x-ray examination when one is searching for other complications. The amount of consolidation is not consistent and sometimes is difficult to differentiate from the lung manifestations of cardiac failure. The microscopic picture is frequently that of hemorrhagic exudation in the alveoli with a false membrane of hyaline eosinophilic material resembling fibrin in the dilated alveolar ducts, not unlike the so-called hyaline membrane of the newborn period. The amount of exudate present usually is very slight and thoracentesis accomplishes little.[1]

Vascular System

Von-Glahn and Pappenheimer[1] described characteristic changes in the small vessels of the lungs, pleura, kidney, perirenal, and periadrenal adipose tissue, ovary, testes, pancreas, sigmoid flexure, and cecum. They described an exudation of fibrin into and about the vessels, destructive changes in the cellular components of the vessel wall, distinctive cellular reaction in the adjacent tissue, and absence of thrombosis. Others have described vascular lesions in the peritoneum, meninges, lungs, small veins, diaphragm, etc. Probably in acute rheumatic fever the vascular system is involved throughout the body and this vascular involvement has a great deal to do with many of the minor manifestations of the disease such as epistaxis and purpuric skin lesions as well as the multiple complaints referable to the joints, muscles, etc.

Coronary Arteritis: Because of the widespread involvement of the vascular system, the coronaries occasionally become involved producing rheumatic coronary arteritis.[5] There is no specificity as to which coronary branch may become involved and the severity and number of branches affected will vary considerably. As in other areas, the smaller branches are the most commonly affected. Pathology varies from simple collarets of Aschoff cells to severe obliterative arteritis. The prolonged and chronic cases may progress to sclerosis and thickening of the arterial wall. The diagnosis of this manifestation is made only when the flow is obstructed enough to cause changes in the myocardium and thereby produce electrocardiographic deviations characteristic of myocardial damage of an ischemial nature. Sudden onset of precordial pain, not relieved by large doses of salicylates, during an acute bout of rheumatic fever, should make one suspicious of involvement of the coronary arteries.

Aortitis: Just as the arteries of the heart are involved, so is the aorta. In rheumatic aortitis, the changes are similar to those found in the smaller blood vessels. The acute lesion, however, usually is healed with scar tissue; thus weakened areas may progress to dilatation and aneurysmal formation. Diagnosis usually is very difficult to establish and should be considered only in the presence of aortic valvular murmurs or when dilatation of the aorta occurs during the illness. It is well to remember that aneurysmal dilatation beyond the stenotic lesion of the aortic valve is possible without the presence of mesaortitis.

Abdominal Manifestations

Abdominal pain is a common symptom of acute rheumatic fever and not infrequently it is so severe that an exploratory laparotomy is performed. Localized peritonitis has been reported with acute inflammatory exudate in the subperitoneal connective tissue as well as fibrinous peritonitis, perihepatitis and perisplenitis. Herschfield[6] reported two cases of segmental colitis associated with acute rheumatic fever. In each instance the pathology of the appendix and the adjacent bowel was that of an indolent inflammatory reaction in the stroma of the serous peritoneal coat with a fibrinoid surface exudation. The inflammatory reaction was of a diffuse character although mild and showed a distinct orientation to the vasculature as one would expect from the previous reports. There was no specific histologic manifestation of rheumatic infection; nevertheless, this type of reaction has been reported many times in the synovial membranes of joints in known cases of rheumatic fever. Rarely one will see occasional cases of liver pathology with vomiting, delirium, acholic stools, etc., during the acute phase of rheumatic fever and in children who present minimal signs of congestive failure, the pathologica changes in the liver are sometimes so severe as to suggest subacute yellow atrophy.[1]

Nephritis

Glomerulonephritis is a frequent accompaniment of acute rheumatic fever. Hartman *et al.*[7] in a well-written report state: "Nephritis occurs somewhat more frequently in patients with rheumatic fever and rheumatic heart disease than is usually suspected, and conversely, involvement of the heart may occur despite predominant involvement of the kidneys in certain cases of nephritis." In their series of reported cases, they found that acute glomerulonephritis and acute rheumatic fever occurred simultaneously in 2.5 per cent of a series of clinically diagnosed acute nephritis and an additional 1.7 per cent had rheumatic heart disease. Three per cent of the rheumatic series studied postmortem had acute glomerulonephritis. Chronic nephritis was present in an additional 2 per cent. In other words, in the total group of nephritis cases 4.2 per cent had acute or chronic rheumatic involvement of the heart while in the rheumatic series, 5 per cent had glomerulonephritis acute or chronic. Therefore, the physician must be astute in his management of the case because of the dangers of the development of glomerulonephritis with the possibility of hypertensive reaction in an already acutely involved myocardium.

Cardiac Involvement

Pericarditis: During the phase of acute carditis, many ancillary reactions make take place within the pericardium. Pericarditis with or without effusion is a frequent accompaniment, and like the diagnosis of carditis itself, the findings change from one examiner to the next. To quote Taran:[8] "It would seem that the cardiodynamics responsible for cardiac sounds and murmurs are in a state of flux in active carditis." Occasionally, the cardiac configuration by x-ray or fluoroscopy will be such that diagnosis can be entertained. The electrical potential in the electrocardiogram will at times give a clue as to the presence or absence of fluid. Again, however, it must be remembered that only when the lesions are of sufficient degree to produce signs and symptoms is one able to make a diagnosis, so that unless the findings are consistent, the diagnosis of anything beyond carditis is rather difficult.

Subacute Bacterial Endocarditis: Although subacute bacterial endocarditis is not a manifestation of the acute phase of rheumatic fever, it nevertheless is frequently found in rheumatic

heart disease and may be associated with an acute exacerbation. It is mentioned at this time merely to plead for the heroic use of penicillin in its management. In those cases due to streptococcus viridans, large doses of penicillin V given orally is sufficient to effect a cure in three to four weeks. In our own experience in culturally proven cases of subacute bacterial endocarditis, in both rheumatic and congenital heart disease, we have been able to eradicate completely the organism by administering 1.5 million units of oral penicillin V every four hours for periods varying from four to six weeks. Needless to say, if the infection is the result of some other organism, sensitivity tests should be done and the appropriate drug instituted. If, however, one is unable to isolate the causative organism and if the patient is suspected of having bacterial endocarditis, then early and adequate treatment should be given despite sterile blood cultures. Holzman[9] feels that this policy might be extended to include patients with active rheumatic fever who are doing poorly or in whom the illness is unduly prolonged.

Cardiac Failure: Occasionally during an attack of acute rheumatic fever, one is faced with the problem of acute right heart failure. In children the chief manifestation of this complication is a tender, enlarged liver. This progresses to ascites, edema of the lower extremities, and finally some lung congestion. If the usual measures of bed rest, oxygen, salt free diet, etc. are not adequate to control the situation, then one is faced with the use of digitalis. There are those who feel that with an active infection of the myocardium, digitalis is not indicated nor is it effective. If, however, one has done everything possible to overcome this complication and is not successful, then in fairness to the patient, a judicious trial of digitalization is indicated. One may also resort to the associated use of diuretics, although this must be done with great caution as there is apt to be a pooling of fluids and then with sudden marked excretion other complications may occur such as mercurial or digitalis intoxication.

Summary

One must think of rheumatic fever as a disease of the collagen system and not of the myocardium alone. If this is done, many of the protean manifestations will not be overlooked.

Involvement of the central nervous system may be manifested by meningoencephalitis, hyperpyrexia or psychotic symptoms. Respiratory system involvement may produce pleuritis and pneumonitis. Vascular lesions may produce coronary arteritis and aoritis. The abdominal manifestations may occur as a result of serous fibrinoid peritonitis.

Glomerulonephritis may occur simultaneously with rheumatic fever in 4.5 to 5 per cent of all cases. Subacute bacterial endocarditis may also be associated with an acute exacerbation of rheumatic fever.

Congestive heart failure is a complication of severe carditis. Great caution must be exercised in the use of digitalis and mercurial diuretics in the presence of active infection of the myocardium.

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Treatment of Rheumatic Fever

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It may seem somewhat unnecessary to say that before one treats a patient for rheumatic fever one should be sure that the patient actually has rheumatic fever. In the writer's experience he has found that 30 per cent of patients that he has seen treated for rheumatic fever did not have rheumatic fever according to the most widely used criteria for the diagnosis of this condition. In a few localities as high as 80 per cent have been wrongly diagnosed chiefly because a single nonspecific sign, such as a low-grade fever, recurrent bouts of fever, a rapid sedimentation rate, a prolonged QTc in the electrocardiogram, a heart murmur, etc., was used to establish the diagnosis. Those patients with a number of highly suggestive symptoms and signs in whom a diagnosis could be made only after a prolonged period of study and observation were not included in the above figures. It is also generally recognized that in spite of a very complete and prolonged study there is still a small group of patients in whom the diagnosis remains permanently in doubt. The main difficulty in diagnosis lies in the fact that there is at this time no specific test, symptom, or sign that is indicative unfailingly of rheumatic fever or "rheumatic activity." Probably the nearest approach to such a sign is the presence of an active carditis in a child with a febrile illness. However, as everyone knows, there are many victims of rheumatic fever who never have a clinically active carditis. The best list of diagnostic criteria is that compiled by Jones and later modified by a committee of the Council on Rheumatic Fever.[1] It might be reemphasized that this list was compiled as a guide only and not as a mathematical formula for adding nonspecific symptoms and signs to make a diagnosis.

This same difficulty in recognizing the "active rheumatic state" is responsible for most of the differences of opinion about the length of time a patient with rheumatic fever should be treated. Naturally, the ideal duration of active treatment should cover the entire period of rheumatic activity and no more. At the present time the actual duration of treatment must depend upon the judgment and experience of the physician in charge who again bases his opinion on a group of nonspecific symptoms and signs. Within these limitations the following is presented as a guide for treatment, based entirely on the experience of the writer and his associates. Many of the dosages and intervals of time used are necessarily arbitrary or didactic and should be changed to meet the needs of the individual patient. No attempt has been made to include or refer to all known theories and opinions of treatment and their omission does not indicate or imply the writer's disapproval of them.

Destruction of Streptococci

At this time most investigators believe that both primary and recurrent attacks of rheumatic fever are caused or precipitated by group A streptococci. Some of the longer illnesses may actually represent a series of infections by various types of organisms of this group. Whether living streptococci necessarily are present in the body throughout the period of rheumatic activity has not been determined. A streptoccal infection of the throat nearly always precedes an attack of rheumatic fever and an increasing ASO titer during the early part of an attack of rheumatic fever reflects such streptococcal infection.

Initial Therapy: In view of these observations and opinions it seems logical that the first step

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in the treatment of an active rheumatic fever patient might be an attempt at the eradication of all living group A streptococci. This is best accomplished by the administration of enough penicillin or its equivalent to produce an adequate blood level for a period of about ten days. If throat cultures, properly taken, remain positive for group A organisms, this level should be maintained for a longer period of time. A negative throat culture during the beginning of the ten days of treatment should not be considered an indication for discontinuing the penicillin therapy. The following doses of penicillin usually are adequate:[2]

(1) One intramuscular injection of benzathine penicillin G (600,000 to 900,000 units for children and 900,000 units for adults).

(2) One intramuscular injection every three days for a total of three doses of procaine penicillin with aluminum monostearate in oil (300,000 units per dose for children and 600,000 units per dose for adults).

(3) One tablet of 200,000 to 250,000 units of penicillin orally four times daily for a full ten days.

In cases of penicillin sensitivity, equivalent doses of other antibiotics can be used, although some of them are somewhat less effective in eradicating group A streptococci than is penicillin. Sulfonamides are not recommended for this purpose as they are only bacteriostatic and not bacteriocidal.

Long-Term Therapy: After this initial treatment and especially after it is felt that all living streptococci have been eradicated the patient should be continued indefinitely on one of the following routines in an attempt to prevent reinfection by this group of streptococci.

(1) Sulfadiazine (or comparable sulfonamide) orally. In patients weighing less than 60 lb, one-half gram once daily usually is adequate, while in patients weighing over 60 lb two doses daily of this amount each, are recommended. Fairly frequent blood counts, especially at the beginning of this regime, are desirable so that any untoward effects of the drug may be detected early. Later an occasional count will suffice. The appearance of rashes also calls for the discontinuance of this procedure.

(2) Penicillin, orally. Two doses daily of 200,000 to 250,000 units each are recommended and will usually prevent reinfection.

(3) Penicillin, parenteral. The intramuscular injection of 1,200,000 units of benzathine penicillin G once each month is highly effective.

(4) In patients who are sensitive to both sulfonamides and penicillin it may be necessary to use one of the broad spectrum antibiotics, even though they sometimes are less effective against group A streptococci than is penicillin.

This program has no curative effect on the episode of rheumatic fever that is already present when this regime is started, nor does it exert any influence on the amount of heart damage associated with the current episode. Its entire function is to prevent as far as possible any additional episodes of rheumatic fever.

Rest

Because the heart is the organ that sustains practically all of the permanent damage in rheumatic fever, logical treatment includes as much rest of the heart as possible while part or all of it is inflamed. Although no satisfactorily controlled large group studies are available to prove that rest minimizes the damage and that work and activity increase the damage, it has been accepted generally that this is so. When the patient has a high fever, rapid heart rate, and appears sick, he should be at complete rest in bed, either flat, or with the head and shoulders slightly elevated. If the carditis is enough to produce some degree of heart failure, the patient may have to be at a 45 degree angle or higher. At this stage he should be fed, bathed, and turned in bed. With proper treatment this stage should not last many days. To continue these severe restrictions for weeks, months, or occasionally years, is unnecessary and may be very detrimental to the child's entire future outlook on life. As soon as the temperature and heart rate are normal or near normal and the patient "feels better," he should be allowed more freedom in getting around in bed, feeding himself, and washing hands and face. In most instances "schooling" at home or in the hospital can be started a few days later.

As soon as all signs of rheumatic activity have disappeared, the patient should be allowed out of bed for increasing lengths of time. At this stage

the physician must exercise great judgment so that he continues to treat a patient and not a sign or laboratory report. For example, the doctor must remember that many children normally have rectal temperatures between 99 and 100. He must not forget that some children, especially if overweight, may normally have a rapid sedimentation rate for months and years and that an ASO titer reading is no guide to rheumatic fever activity. In the writer's experience, many more patients are restricted too long rather than too short a time.

Because rheumatic fever may be present a long time, the mental reactions and attitudes of a patient to his illness are most important. It is most unfortunate indeed when a patient develops a permanent invalid reaction because of the treatment he receives while ill.

As soon as the physician thinks that the rheumatic activity has ended, the patient should be allowed to get out of bed and gradually to resume his normal activities. Ideally, the temperature and heart rate, the joints and the skin, the blood count, the sedimentation rate, the C-reactive protein, the acute changes in the electrocardiogram, etc., should be normal before the patient is allowed to get out of bed to engage in the milder types of activities. When one or more of these signs remain abnormal, the physician must decide whether they represent rheumatic activity, some other illness, or mere variations from the normal. In most instances the patient can return to school or to work within a very few weeks after this time. The problem of continued restriction will be discussed later.

Drugs

ASPIRIN

In treating rheumatic fever, two general groups of drugs are available, the salicylate and the hormone group. There are others, but they will not be discussed here. The salicylate group has been used for a much longer time than the hormones. Aspirin (acetylsalicylic acid) is the usual salicylate used and is given in large doses early in the illness. One grain per pound is generally considered the optimal beginning dose with a maximum total of 150 to 180 gr in a 24-hour period, given in divided doses. If the patient cannot tolerate this amount, the largest tolerated dose is given. However, as the dose given decreases from the ideal or calculated amount, the number of failures with this drug increases. In most instances the fever decreases and acute painful joints disappear rapidly. The patient looks and feels better. The heart rate decreases. In the more favorable cases this occurs in 24 to 72 hours; in the less favorable cases the time necessary to produce this change may approach one week. If the patient is very sick and can take the calculated adequate amount and there is no indication of improvement in 48 to 72 hours, the patient should be treated with one of the hormone preparations with or without aspirin. After three days of aspirin therapy (two days if the response is marked) the dose can be reduced by one-fourth. If progress continues satisfactorily for an additional five to seven days, the original dose can be cut in half. After an additional two weeks of satisfactory progress the dose can be decreased in steps of 10 gr at four to seven day intervals. Should there be any sign of recurrence of symptoms, the dose can be doubled or increased enough to control the symptoms and signs. When this has occurred, a new reduction of dosage in steps can be instituted.

Obviously, this scheme of dosage is highly arbitrary and is described to serve as a guide only. If the attack of rheumatic fever is very mild and there is no clinical evidence of carditis, the duration of each step can be shortened, whereas a severe or complicated episode may require the duration of each step to be increased. Some of the complications of using aspirin are nausea, vomiting, abdominal cramps, deafness, hemorrhages, and hyperventilation (commonly but erroneously called "acidosis"). The occurrence of these symptoms at doses smaller than the "effective level" may force the use of hormones for the treatment of any particular attack.

HORMONE TREATMENT

About 1949 two interesting compounds for the treatment of rheumatic fever became available, ACTH and cortisone, commonly called "the hormones." Since then there have been several excellent reports dealing with the results

obtained by the use of these preparations and their derivatives and modifications.[3,4] These preparations can produce dramatic results but, on the other hand, they are by no means without danger.[5] Because they can be given orally, cortisone, hydrocortisone, prednisone and prednisolone are the ones most commonly used. The following plan of dosage generally has been followed by the writer and the staff of the Weiting-Johnson Hospital for children with rheumatic fever.

When cortisone or hydrocortisone is used, 300 mg are given the first day (75 mg every six hours). For the next four days the patient receives 200 mg daily (50 mg every six hours). From then on each dose is reduced by five mg (a reduction of the daily dose by 20 mg) every four days provided the patient remains asymptomatic. If any signs of rheumatic activity recur, the dose is increased one or two steps to the amount that again controls the symptoms or signs of activity. When this occurs, the step-like reduction every four days is resumed. In this way an amount approaching the minimum necessary to control the disease is utilized.

If prednisone or prednisolone is used, a similar step-like reduction every four days is employed. The initial dose is generally 80 mg during the first 24 hours divided into four doses of 20 mg each, every six hours. For the next four days the total daily amount is 40 mg divided into four equal doses at six hour intervals. From then on the total daily dose is reduced by five mg every four days. After the 20 mg daily dosage period, the dose is reduced to five mg every eight hours for four days, then five mg every 12 hours for four days, and, during the final four day period, five mg once daily.

Many times when the hormones are discontinued, especially when discontinued rather rapidly, there is a "rebound period" during which recurrence of fever, tachycardia, and some of the other symptoms and signs may reappear, but these usually disappear in a few days. If they fail to regress, the patient requires additional treatment. Many times, merely repeating the last three or four steps of the preceding schedules may suffice. The very gradual tapering off in this schedule reduces the number of rebound episodes observed. There is theoretic advantage to administration of several doses of ACTH during each of the above treatment schedules to stimulate the adrenal to resume all of its functions when the cortisone and prednisone, etc., are withdrawn.

Cortisone and prednisone, etc., tend to hold sodium and water in the body, thus throwing an additional burden on the circulation and possibly precipitating frank congestive failure. The advantage of prednisone over cortisone is that a smaller milligram dose is required and, as the water and sodium retention seems to vary directly with the milligram dosage, there is less retention with prednisone. To further combat this action the patients are put on an 800-mg sodium diet and are given 1 g of potassium chloride three times daily during the period of hormone treatment.

Schedules similar to that of cortisone and prednisone can be used in administering ACTH. Roughly 1.0 to 1.5 international units per pound of body weight should be the starting dose. If the lyophylized preparation is used the daily dose should be divided into four intramuscular injections with six hours between injections. With the ACTH-gel, the number of injections per day may be reduced to two. The same sodium intake restriction and potassium chloride addition are also of value when ACTH is used. Because of the greater ease and comfort of the oral administration of cortisone and prednisone over the injection of ACTH, the writer has used very little of the latter preparation. Many other clinics and studies appear to have adopted the same routines. The two groups of preparations probably are equally effective if properly used.

Nearly all the patients treated by hormones develop a "moon-face." Many, in addition, develop hirsutism, striae, or acne. Other side effects sometimes noted are increase in blood pressure, glycosuria, infections (especially around the toe nails), mental changes, increased appetite, and marked gain in weight. One patient manifested diffuse inflammatory lesions of the skin and subcutaneous tissues. Other complications such as convulsions, renal hemorrhage, hepatomegaly, pigmentation, etc., have been reported in the literature.

The presence of congestive failure due to rheu-

matic carditis calls for special care in treatment. The hormones need not be withheld, but if used, the patient must be under very close observation and sodium restriction must be followed conscientiously. Mercurial diuretics may be required to remove salt and water from the body. If digitalis is used the dose should be calculated according to the body weight and no attempt should be made to give enough to get clinical digitalis effects. The writer believes that digitalis has little or no effect on the heart in the presence of active rheumatic carditis and large doses may injure the patient by adding digitalis intoxication to his difficulties. On the other hand, digitalis in the presence of congestive failure when there is no active carditis usually is effective and is a most valuable medication.

There is no intent to discuss the relative merits of aspirin, ACTH, or the cortisone group in this paper, or to speculate as to their modes of action, or their effect or relative effectiveness on the prevention of permanent cardiac damage. Studies over longer periods when available should give the answers to these aspects of treatment. The writer believes that all three groups, aspirin, the cortisone group, and ACTH, do shorten the course of an attack of rheumatic fever greatly and do reduce the amount of cardiac damage, probably all to the same degree. However, the response to the hormones is usually more prompt and dramatic than to aspirin.

Congestive Failure

Some of the aspects of congestive failure in patients with rheumatic fever have already been mentioned but elaboration may be of interest and value. The writer is in accord with the widely held opinion that congestive failure in a child with rheumatic heart disease is due always to rheumatic activity. He also feels that the same is true in adults except that in adults it is not possible always to be sure that the patient does not have some additional type of heart disease such as arteriosclerotic heart disease, thyroid heart disease, etc., which may be responsible for the congestive failure, while the rheumatic heart disease may be entirely inactive at the time. A number of adults with rheumatic heart disease and congestive failure have been seen whose failure at first had not responded to the usual anticongestive failure treatment (digitalis, salt restriction, diuretics, rest, etc.) but who later needed no cardiac medication of any kind to remain in a well-compensated state. Some of these patients had a few suggestive signs of active rheumatic fever, such as a slight elevation in temperature, mild migrating arthritis or arthralgia, increased P-R interval, partial or complete heart block, unexplained anemia, etc., while others had signs attributed to congestive failure only. The writer feels that these patients were in failure because of active rheumatic carditis and that when the rheumatic activity ended the failure disappeared too.

Because of these experiences, the writer believes that when rheumatic activity is present in patients with congestive failure it is of prime importance to treat the rheumatic activity by rest, salicylates, hormones, etc., taking added precautions against sodium and water retention which in itself could easily aggravate the congestive failure. In such cases, salt restriction and potassium chloride administration should always be prescribed. In the writer's opinion mercurial diuretics are of more value in this situation than is digitalis, although digitalis is given sometimes in doses that by calculation should produce digitalization. Anticoagulants to reduce the danger of thrombosis and embolization may be of value but have not been used by the writer. No attempt was made to restore normal rhythm by use of quinidine in the presence of acute carditis with congestive failure.

Long-Term Management

No account of the treatment of rheumatic fever is complete without a few words on the long term management of a person who has had a rheumatic attack. In general, individuals who have had rheumatic fever of any degree of severity and who have sustained no clinically demonstrable heart damage need not be restricted in any way after a very few weeks after the end of their acute illness. This applies even to competitive sports and athletics. It may be very harmful psychologically to children in this group to excuse them permanently or for several years from the regular physical educational activities in school. If there is residual heart damage, each case must be carefully and individually

considered. The general tendency today is to over-restrict these people. As a rule, patients who have either mitral or aortic insufficiency without demonstrable left ventricular enlargement, need little or no restriction. These patients are asked to avoid competitive sports of the basketball or football type, although there is no definite evidence that such exertion is harmful. To meet insurance requirements and to avoid medico-legal situations children with these lesions are excluded from all competitive sports in school. If there is some left ventricular enlargement with either of these two lesions, the amount of restriction varies more or less with the amount of enlargement.

In persons who develop mitral stenosis the relationship between heart size and exercise is not as clear-cut, since the left ventricle does not enlarge. The amount of restriction is related to the increase in pulmonary circuit pressure. Although there is no definite evidence that exertion accelerates the onset of cardio-pulmonary insufficiency, it seems reasonable to assume that it does. It is wise therefore to restrict these persons to ordinary moderate activities of life and to ask them to avoid strenuous or prolonged exertions even if such activities appear to be well tolerated.

In aortic stenosis, no great restriction of activities is required unless physical, radiologic or electrocardiographic indications of hypertrophy of the left ventricle appear. In older patients, coronary insufficiency is more common in the presence of aortic stenosis than in its absence, possibly due to the involvement of the mouths of the coronaries by the same disease process. When more than one valve lesion is present, a composite picture results and the recommendation must also be of a "composite type" influenced chiefly by the dominant lesion. These suggestions apply only to persons who have evidence of rheumatic heart disease but who are free of any signs or symptoms of cardiac insufficiency.

The writer feels that in most instances the greater threat to the health and life of the person who has rheumatic heart disease is not from the valvular lesion but from recurrence of rheumatic activity which can increase the cardiac damage. It is therefore of the utmost importance that the patient follow a regime for the prevention of such recurrences by one of the methods described earlier in this paper. The writer feels that these measures should be continued throughout the person's life. If conscientiously followed without any lapses, the amount of protection obtained by such a regime is very great.

Surgical Treatment

During the last few years, great strides have been made in the surgical treatment of heart conditions, including the valvular lesions produced by rheumatic fever. Of the four lesions mentioned above, the surgical treatment of mitral stenosis has been by far the most successful. Surgical treatment of the three other lesions is still in the experimental or developmental stage. In the writer's opinion, the presence of a typical murmur of mitral stenosis, even though loud or long, is not in itself an indication for surgery. However, when evidence of increasing pulmonary artery tension appears with such symptoms as dyspnoea on slight exertion, hemoptysis, pulmonary edema, or such signs as accentuated pulmonic second sound, enlarging left auricle, hypertrophy of the right ventricle, then surgical treatment is indicated and can offer the patient considerable relief and protection.

Mode of Life

One of the unfortunate complications of rheumatic fever is the development of a cardiac neurosis or an invalid reaction which in some instances is even more disabling than the organic heart diesase that may be present. Only too frequently part of the responsibility for this condition can be laid at the door of the attending physician. It may be due to unnecessarily prolonged or severe restriction during or after the acute attack, failure to explain the nature of the condition to the parents or family of the patient so that they overprotect him, or to overemphasis of morbidity and mortality rates.

Most children are able to attend and should attend regular classes in regular schools. If kept in special classes or special schools unnecessarily, the constant reminder each day that they are abnormal may do a great deal of mental harm. Unjustified exemption from physical education classes may have the same effect. It becomes ludicrous when a child is restricted in school but is entirely unrestricted outside of school. This

situation may lessen a child's respect for school and other authority.

In young adults, rejection for military service, refusal or "rating" by insurance companies, and increased difficulty in obtaining employment may be very disturbing and lead to invalid or panic reactions. Proper explanation of the nature of their illness and condition to them in advance helps to prevent such reactions.

The common interpretation of State Compensation Laws has interposed an unnecessary and unfortunate, even if unintentional, barrier to many persons with easily detectable rheumatic heart lesions. Many large corporations requiring pre-employment physical examinations, categorically reject such applicants because of the greater medico-legal liability, despite majority medical opinion which favors the grading and employment of such persons and feels that many kinds of work will contribute nothing to a cardiac breakdown. Although an individual physician has no control over this state of affairs, he can warn his patients of what may happen and why. He may be able also to suggest other fields of employment where the reception is less hostile. In many instances this reorientation for employment, as well as for some types of professional and special education, can be started as early as the later grammar school days. For example, a young girl who has very definite rheumatic heart disease who is entering high school and wants to become a nurse should be interested in some other type of work where a pre-entrance physical examination will not demolish her ambition of years' standing.

Marriage and pregnancy should not be interdicted in any young woman who has rheumatic heart disease who has been able to do light physical work and who has never been in failure. Furthermore, pregnant women who already have been in failure may get along surprisingly well if treated very carefully. Nevertheless, pregnancy should be avoided if there is or has been a definite episode of congestive failure due to residual cardiac damage itself.

No special hazard in air travel exists for patients with rheumatic heart disease who have never been decompensated or who at the time of the flight are in a good state of compensation. Patients who have dyspnoea on very slight exertion or are in definite failure may have an increase in their symptoms at the higher elevation and preferably should avoid such travel.

Summary

(1) The treatment of rheumatic fever may be difficult because of the absence of a definite test for the diagnosis of this disease and for the determination of the cessation of "rheumatic activity."

(2) It is of prime importance to destroy any living group A streptococci in the body and to prevent any reinvasion by these organisms.

(3) Rest is an important part of the treatment, but it is very frequently needlessly severe and prolonged.

(4) Aspirin, the cortisone group of hormones, and ACTH in adequate dosage are all effective in relieving the clinical symptoms of rheumatic fever and these drugs probably reduce the amount of permanent cardiac damage. Aspirin is less dramatic in its results but important complications are fewer.

(5) Congestive heart failure in the presence of active rheumatic carditis calls for special therapeutic measures.

(6) It is important to give the patient some insight into his condition to prevent neurotic, invalid, and panic reactions and to help him meet some of the problems of life related to his condition.

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Clinical Studies

Acute Nonspecific Pericarditis*

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ACUTE nonspecific pericarditis has been recognized for a century.[1] Not until Barnes and Burchell[2] focused attention on this syndrome were other notable contributions made.[3–17] Four investigations[4–7] included a follow-up study. Other studies[8–11,16] drew attention to the frequent occurrence of pleurisy associated with pericarditis. In this communication we stress the clinical features, the association of preceding respiratory infection, and the differential diagnosis. The onset was relatively acute and was characterized by pleuritic type of pain often aggravated by deep breathing, body movement, or coughing. Chest pain, fever, increased sedimentation rate and serial electrocardiographic changes were common to all patients.

MATERIAL AND METHODS

The criteria for selection of patients were: (1) absence of a history of rheumatic fever, rheumatic heart disease, tuberculosis, uremia, myocardial infarction, or any collagen disease; (2) the presence of a pericardial friction rub, or changes in the serial electrocardiograms compatible with the diagnosis of pericarditis. Of 158 patients with pericarditis admitted between 1950 and 1956, only eighteen satisfied these rigid criteria and were available for follow-up study. Twelve-lead electrocardiograms were made on all patients during the acute illness, and at one, three, four and five years subsequent to the initial observation. Two-meter roentgenograms of the chest were made during the acute illness and at the end of the study. Antistreptolysin-O titer was measured according to the method of Rantz and Randall.[19] Blood cultures and throat cultures were taken prior to therapy.

OBSERVATIONS

Clinical Signs and Symptoms: The patients ranged from 21 to 68 years of age. Fourteen were in the fifth and sixth decade and two in the seventh. Males were predominant, in a ratio of nine to one, as noted also by others.[4,6] An upper respiratory infection manifested by sore throat, tonsillitis or coryza preceded the onset of the disease in fourteen. The early clinical signs and symptoms were tabulated as follows:

Antecedent respiratory infection	16
Chest pain	18
Substernal pain	12
Dyspnea	9
Pericardial rub	15
Fever	18
Abnormal electrocardiogram	18
Pneumonia	9
Pleural effusion	4

Chest pain was common to all. The pain was pleuritic in character, stablike, and frequently aggravated by respiration, cough or sudden body movement. The pain was retrosternal in 12 instances, associated with substernal soreness unaccompanied by shock and not aggravated by walking. Distribution of pain is shown in Figure 1.

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As originally emphasized by Barnes and Burchell,[2] the pleuritic character of the pain without shock was an aid in differentiating this syndrome from acute myocardial infarction. Furthermore, the early appearance, disappearance and reappearance of the pericardial friction rub was a differential diagnostic characteristic in contrast to the delayed appearance and short duration of the friction rub which is less often heard in acute myocardial infarction.

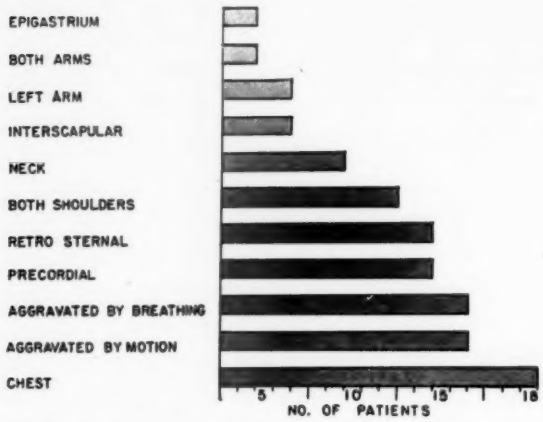

Fig. 1. Distribution of pain in 18 cases of nonspecific pericarditis.

Shortness of breath was noted in nine patients, apparently related to the severity of the pleural and pericardial pain. Fever, leukocytosis, and elevation of the sedimentation rate appeared simultaneously or preceded the onset of the pericardial friction rub. Temperature range was between 100° F and 104° F, varying in duration from 5 to 30 days. Accelerated sedimentation rate was common to all, persisting as long as eight weeks in five patients. Leukocyte counts varied from 7,000 to 17,500.

X-ray Signs: Two-meter roentgenograms of the chest, taken early in the course of the disease, showed an enlarged cardiac silhouette in ten instances. All receded to normal size without pericardicentesis (Figs. 2, 3). Radiologic evidence of pleural effusion was found in four patients. Transient parenchymatous infiltration of one or both lungs was noted in nine patients.

Electrocardiographic Changes: All serial electrocardiograms showed changes compatible with pericarditis, with a ventricular rate greater than 80. The electrocardiographic pattern of acute pericarditis has been described by Barnes and Burchell[2] who have clearly distinguished the changes of pericarditis from QRS—T alterations associated with acute myocardial infarction. In our study, abnormalities appeared in multiple leads, consisting of elevation of the RS-T segment with upright T waves during the initial phase with the S wave displaced upward. Elevation of the RS-T occurred in every patient, when the record was taken during the first week, and persisted for 4 to 12 days. (Figs. 4, 5.) These RS-T segments were characterized usually by being concave upward. The T wave became low, flat, or inverted, concomitant with the lowering of the RS-T segment to the isoelectric line. AVR showed reciprocal depression of the RS-T segment with sharp inversion of

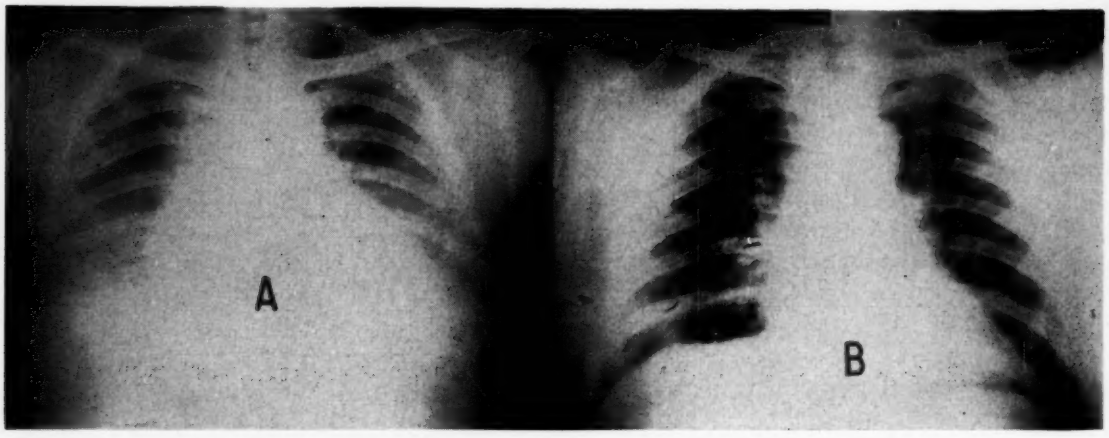

Fig. 2. A shows enlarged cardiac silhouette on 6/20/50. B shows normal cardiac contour on 7/2/50.

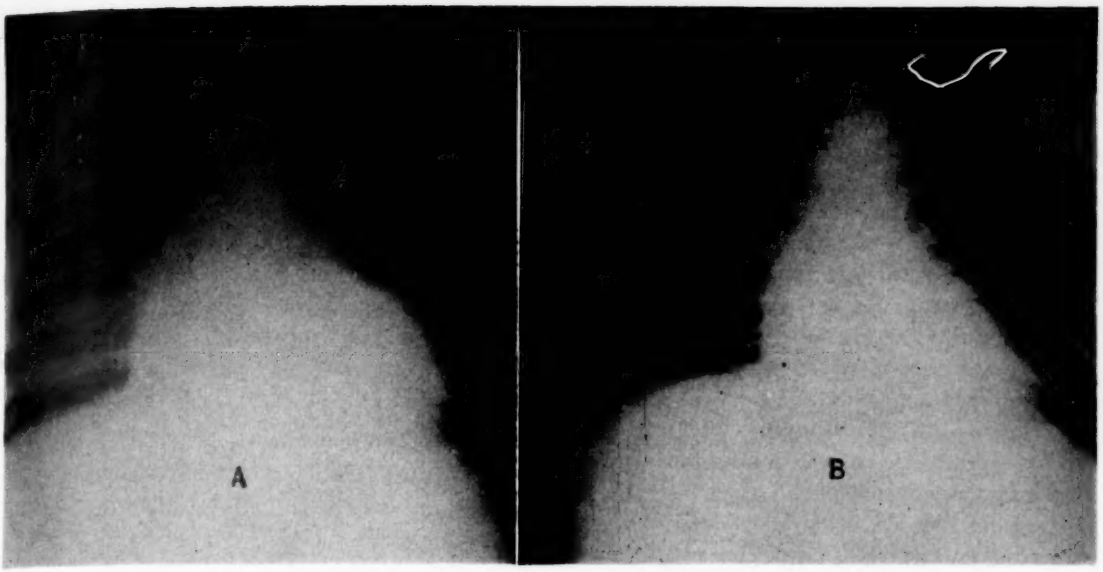

Fig. 3. A shows enlarged cardiac silhouette with pneumonia on 3/4/56. B shows normal cardiac contour and clear lung fields on 3/21/56.

the T wave. In no instance have we observed the reciprocal RS-T alterations in standard leads I and III, nor abnormal Q waves which are characteristic of myocardial infarction. There were four patients who failed to show the early RS-T elevation. Their original electrocardiograms recorded during the second week of the disease showed flat T waves in standard leads

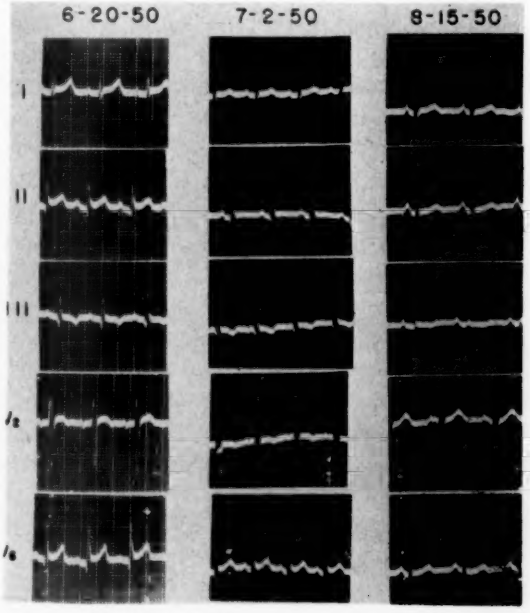

Fig. 4. Electrocardiograms show serial changes compatible with pericarditis. Note RS-T elevation with upward concavity in leads 1, 2 and V6 on 6/20/50. On 7/2/50 T is isoelectric in 2, RS-T is still elevated in V6. On 8/15/50 the ECG is normal. Chest x-ray of this patient is shown in Figure 2.

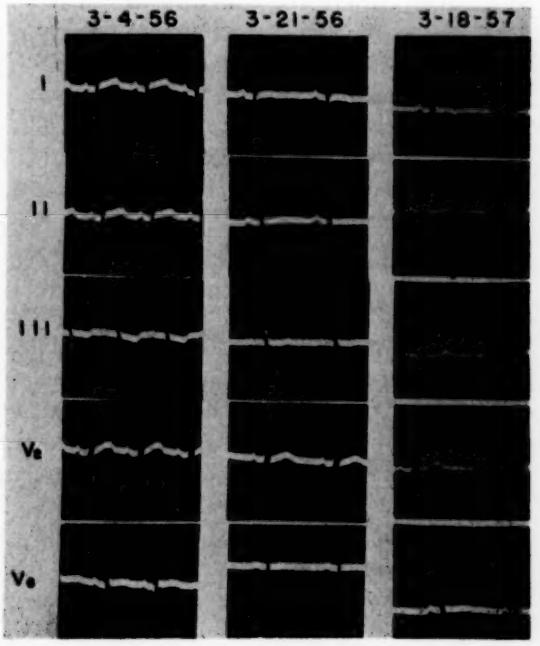

Fig. 5. Electrocardiograms show changes of pericarditis. T is inverted in lead 1 and isoelectric in V6 after one year. Chest x-ray of this patient is shown in Figure 3.

I and II. The appearance of RS-T elevation in a particular lead depends on the axis of the lead, the position of the heart, and the extent of the subepicardial injury. The wide distribution of RS-T segment changes in the unipolar leads was in marked contrast to the commonly localized distribution of the RS-T alterations subsequent to myocardial infarction.

Effect of Treatment: Aspirin, streptomycin, terramycin, penicillin and corticotropin, alone or in combination, were given a therapeutic trial. Seven patients who received aspirin as the sole medication recovered as did nine who were given antibiotic therapy, and two who received steroid therapy in addition to aspirin. Two patients who received corticotropin beginning on the 10th and 14th days of their disease, respectively, after the pericardial rub had disappeared, were relieved of chest pain, but the tachycardia persisted for ten and seven days, respectively.

Comment

The differential diagnosis between myocardial infarction and acute nonspecific pericarditis was made by certain salient features. The majority of our group had upper respiratory infection accompanied by or preceded by pain of pleuritic character, fever, leukocytosis, and elevated sedimentation rate. The most pertinent criteria were, however, the pericardial friction rub and the serial electrocardiographic changes.

The etiology is obscure. An upper respiratory infection preceded the friction rub in 16 of 18 patients. There was an interval of 7 to 14 days between the infection and the clinical detection of pericarditis. Similar to the chain of events in the etiology of acute nephritis, the pericarditis may be an immune response to the invading infection. Our bacteriologic studies and those of other investigators[4–6] showed negative cultures of the blood and of the pleural and pericardial fluids, indicating that actual invasion of the pericardium by the infectious agent did not occur. In our group antistreptolysin titers were not elevated during the acute phase of the disease, but virus cultures were not made. Acute nonspecific pericarditis does not appear to bear any relationship to tuberculosis. Patients with tuberculous pericarditis have a prolonged stormy course with edema, shortness of breath, greatly enlarged heart and distended neck veins. These clinical features are in bold contrast to those of nonspecific pericarditis. Furthermore, serial electrocardiographic changes are also in contrast. T wave inversion persists in multiple leads in tuberculous pericarditis[18] whereas in acute nonspecific pericarditis the T waves usually become upright within a few weeks. To this observation we have noted two exceptions.

Prognosis

Complete recovery was recorded in our follow-up studies. A favorable outcome has been noted by other investigators.[4–7] None has developed constrictive pleuritis or constrictive pericarditis. In recurrent attacks of four patients, two were preceded by respiratory infection, and again no evidence of rheumatic heart disease was observed.

Summary

Unidentified infection of the respiratory tract preceded the onset of acute nonspecific pericarditis in 16 of our 18 patients. Chest pain and pericardial friction rub occurred almost simultaneously or preceded the appearance of fever, leukocytosis, and elevation of the sedimentation rate. Serial electrocardiograms with or without a pericardial friction rub clearly made the differential diagnosis between acute myocardial infarction and acute nonspecific pericarditis. None of the therapeutic agents proved specific. Complete recovery was recorded in all. In the follow-up study there was no evidence of constrictive pericarditis, constrictive pleuritis, residual rheumatic heart disease, or enlarged cardiac silhouette.

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Newer Laboratory Aids in the Differential Diagnosis of Acute Pericarditis

With Particular Emphasis Upon the Value of the Fibrinogen Polymerization Test

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ACUTE pericarditis when not associated with acute rheumatic carditis, uremia, acute myocardial infarction or neoplastic disease is a relatively uncommon disease. Its importance lies, in part, in its close clinical resemblance to other prognostically more serious illnesses, particularly myocardial infarction, and in the elusiveness of its etiology often defying the exhaustive use of all conventional laboratory procedures.

Among newer laboratory tests of possible usefulness in the diagnosis of this condition are the nonspecific indicators of inflammation or necrosis, such as the C-reactive protein (CRP), the plasma fibrinogen concentration, the level of serum glutamic oxalacetic (SGO)- transaminase, and the semispecific fibrinogen polymerization test.

The present report deals with serial studies of these procedures in patients with acute pericarditis undertaken in order to determine their usefulness in differential diagnosis and to evaluate their applicability as guides to the efficacy of therapy of this disease.

METHODS

The fibrinogen polymerization test is based on a previous observation made by Losner and Volk[7] that considerable amounts of fibrinogen are still detectable in serum two hours after gross coagulation when minimal amounts of heparin are added to whole blood (8 μg/3 cc). This phenomenon was subsequently elaborated into a procedure termed the fibrinogen polymerization (F.P.) test.[8] This method has yielded in our hands results uniformly positive in active rheumatic fever, rheumatoid arthritis, chorea minor, and during the early phase of acute glomerulonephritis. A preliminary study of idiopathic myocarditis and pericarditis also revealed positive results during the acute phase of these conditions.[9,10]

The CRP determination was carried out according to the method of Tillet and Francis[1] and that of the Erythrocyte Sedimentation Rate (ESR) by the method of Wintrobe and Landsberg.[2] The Antistreptolysin-O (ASO) titer was determined according to the procedure of Rantz and Randall[3] and the SGO-transaminase by the method of Karmen *et al.*[4] The plasma fibrinogen level was measured according to the clot density method of Losner and Volk[5,6] which is based upon the increasing optical density of coagulating plasma.

RESULTS

Figure 1 summarizes the data obtained in 11 patients with pericarditis. Seven of these had idiopathic pericarditis which was acute in five and subsiding in two patients. Three patients

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† Dr. Losner died January 14, 1957.

suffered a relapse thus permitting the observations of a total of eight acute and two subsiding episodes of idiopathic pericarditis. Two patients had so-called rheumatic pericarditis, i.e., pericarditis associated with rheumatic valvular disease. Two additional patients had presumptive tuberculous pericarditis. One patient had early constrictive pericarditis, the other a hemorrhagic pericardial effusion and evidence of old apical tuberculosis. Histologic examination of the pericardium removed in the first patient showed granulomatous lesions consistent with tuberculosis. In neither patient did bacteriologic examination of tissue and/or pericardial fluid yield tubercle bacilli.

The initial determination of the F.P. test gave consistently positive results in the acute phase of nonspecific pericarditis correlating well with the uniformly accelerated ESR and the plasma fibrinogen concentration but poorly with the CRP and the ASO titer.

The F.P. test was also positive in acute rheumatic pericarditis. It correlated well with the ESR and CRP but poorly with the plasma fibrinogen concentration and the ASO titer.

In the presumably tuberculous group the F.P. test was negative as were all other tests except the ESR.

In serial determinations extending over a period of up to 12 months the F.P. test reflected closely the clinical course of idiopathic pericarditis. Similar observations were obtained in the two cases of rheumatic pericarditis of this series in agreement with our previous experiences.[8]

There was also close correlation between the F.P. test and the clinical manifestations of pericarditis, such as pain and between the F.P. test and the electrocardiographic changes as well. We have noted, furthermore, that the F.P. test remained positive until all clinical manifestations of activity of the disease had disappeared while the acute phase reactants usually reverted to normal at an earlier date. In several instances when the F.P. test remained positive for a prolonged period, a recurrence of the acute pericarditis was observed and with it a return to abnormal of the acute phase reactants.

In contrast to the results of all these procedures, those of the F.P. test were not suppressed by steroid therapy.

Figure 2 illustrates the observations obtained in a typical case of recurrent idiopathic pericarditis. This case demonstrates not only the difficulties of etiologic differentiation but also the effect of various types of therapy upon the clinical and laboratory findings in this disease.

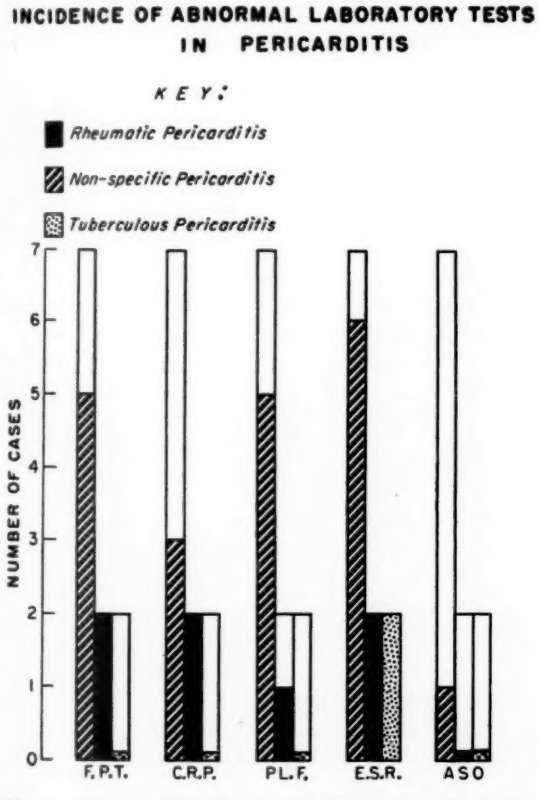


Fig. 1. The total height of each column represents the total number of cases.

Case History

A 32-year-old white male was admitted to the hospital in 1956, because of severe sharp chest pain radiating to the left shoulder and back, aggravated by deep respiration and associated with fever, night sweats, anorexia and slight dyspnea. He had had similar episodes of varying severity and duration since 1943, recurring two to four times yearly since 1945. These attacks were diagnosed as pleurisy or pneumonitis but the exact cause was never established. The positive findings on examination were a bilateral hydrothorax and a pericardial effusion with a friction rub, gallop rhythm, and electrocardiographic changes of acute pericarditis. These findings were associated with fever and a positive first strength tuberculin test. A most extensive workup failed to yield any clue as to the etiology. During the first five days no specific therapy was given so that various cultures and other

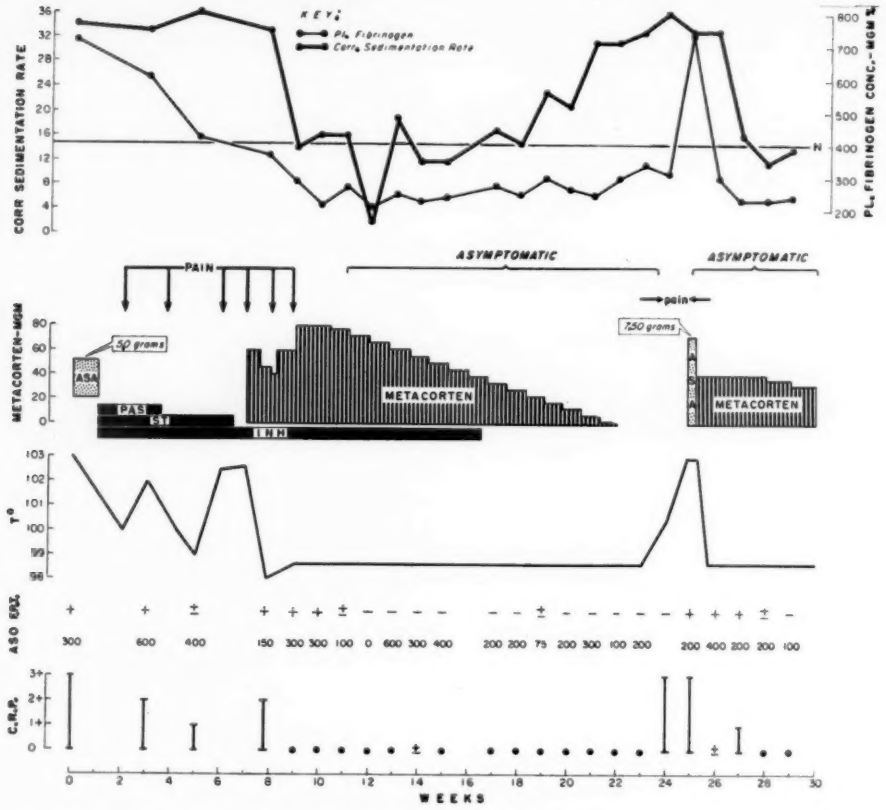


Fig. 2. Graph demonstrating the correlation of the F.P. test, the acute phase reactants and the ASO titer with the temperature, chest pain, and the therapy used in a patient (S.R.) with recurrent idiopathic pericarditis.

laboratory studies could be performed. From the fifth hospital day on, six g of aspirin were given daily for three days without effect. Because it was felt that this patient might have tuberculous pleuritis and pericarditis anti-tuberculous therapy was then instituted with isoniazid (INH), streptomycin and para-aminosalicylic acid (PAS).

Initially, the patient appeared to respond to this therapy with improvement of symptoms and decline in temperature. However, subsequently he again became markedly febrile with extreme chest pain and malaise. At this point drug sensitivity was considered as a possible explanation but was quickly discarded when the recurrence of the pericardial and pleural effusions was noted roentgenographically. The patient was placed then on 60 mg of prednisone daily. This treatment resulted in a dramatic response of fever and of symptoms. On gradual reduction of prednisone there was a moderate re-exacerbation of the pleuropericardial symptoms although he remained afebrile. At this time, prednisone was increased to 80 mg with complete disappearance of symptoms as before. Also all acute phase reactants and the ASO titer became normal again. On the other hand, the F.P. test remained positive for another three weeks before turning negative. At the same time the anti-tuberculous regimen was discontinued. On prednisone therapy not only was there complete disappearance of the patient's abnormal symptoms but the chest x-ray and ECG reverted completely to normal.

The patient was discharged on a maintenance dose of prednisone which was gradually reduced. He was asymptomatic until four days after the last dose of prednisone when he developed myalgias and arthralgias, gradually increasing fatigue, aching anterior chest pain exacerbated by coughing and deep respiration, and chills. When readmitted to the hospital he had tachycardia, a faint gallop rhythm, and again electrocardiographic changes suggestive of recurrent pericardial involvement.

These findings as well as the recurrent fever were associated again with abnormal acute phase reactants and a positive F.P. test. There was no clinical change during an observation period of six days and during subsequent treatment with 8 g of aspirin daily for four days. Forty mg prednisone again promptly abolished the fever and symptoms and caused return to normal of the acute phase reactants. The F.P. test lagged again in its return to normal. He was discharged on steroid maintenance with gradual reduction of the dosage over a two-month period and has remained asymptomatic during this and a subsequent three-month period.

COMMENT

This case seems to confirm the value of the F.P. test as a useful aid (1) for the diagnosis of the nonspecific variety of acute pericarditis, (2) for the evaluation of continued activity of the disease, and (3) for the efficacy of treatment.

The fact that the F.P. test is positive in the acute phases of all observed cases of idiopathic pericarditis and reflects the course of this disease as consistently as it does in active rheumatic fever, as previously reported,[8] suggests a common underlying mechanism which interferes with the normal polymerization process of fibrinogen. The negative F.P. tests observed in collagen diseases and in allergic conditions[9,10] seem to support the hypothesis of an etiologic kinship between idiopathic pericarditis and rheumatic fever. It is mere conjecture, however, whether so-called nonspecific pericarditis is indeed a "rheumatic" disease or represents a "hypersensitivity" reaction.

The experimental production of the localized Shwartzman reaction and of glomerulonephritis in rabbits by the use of nephrotoxic serum has also yielded a very high incidence of positive F.P. tests.[10,11] These observations are in accordance with the view of those who consider these experimental phenomena analogous with the pathogenetic mechanism responsible for acute rheumatic fever and also for acute glomerulonephritis.

As regards the cases of presumptive tuberculous pericarditis, a negative F.P. test was obtained in the patient in whom the excised pericardium furnished histologic evidence of granulomatous lesions with caseation consistent with tuberculosis. This observation suggests that a negative F.P. test may help to rule out a rheumatic or idiopathic pericarditis. It would be most desirable to obtain data on patients with acute pericarditis of bacteriologically proved etiology in view of the therapeutic and prognostic considerations involved.

A review of the literature leads us to believe that at least some of the reported cases[12] of tuberculous pericarditis have been so classified on tenuous grounds, such as the eventual development of constrictive pericarditis. The latter has been recently reported in patients with rheumatic and idiopathic pericarditis.[13–15]

The fact that the F.P. test is not readily suppressed by steroid therapy is of considerable practical significance in view of the excellent results that may be obtained with this treatment in idiopathic pericarditis, and the known suppressing effect of steroids upon the acute phase reactants which renders them valueless as guides during such treatment. Thus the F.P. test can indeed provide a criterion for the serial assaying of the activity of the disease process even during steroid administration.

Differential Diagnosis

As regards the differential diagnosis of acute pericarditis from the most common and serious disease to which it bears clinical resemblance, or myocardial infarction, the most helpful laboratory procedures in addition to the F.P. test which is negative in myocardial infarction,[7,8] are the plasma fibrinogen concentration,[16] the SGO-transaminase[17] and the serum aldolase.[18] In general, in cases of extensive, usually transmural, myocardial infarction all three of these blood constituents are elevated[17,19] while in acute pericarditis only the plasma fibrinogen may be increased, the other two remaining usually within normal limits. Myocardial infarction, however, confined to the intramural or to the subepicardial region may be hard to distinguish electrocardiographically and by laboratory tests from acute or subacute pericarditis. This difficulty may be further increased by the presence of atypical symptoms and by the lack of characteristic findings on physical examination.

This problem is exemplified by the following case history:

A 32-year-old patient (A. Z.) (Fig. 3) was admitted to the hospital because of intermittent chest pain of 18 hours' duration. He had been well until the day before admission when while working he noted gradual onset of sharp, sticking substernal pain which later radiated to the left anterior chest, shoulder, and arm and eventually also straight through to the back and to the neck. The pain was accentuated by deep respiration. The patient had two more episodes of pain unrelieved by narcotic injection given by his private physician. About three months previously he had an episode of irregular palpitations and following this had several episodes of anterior substernal numbness starting in the left shoulder with no strict association with exercise or excitement. The episode would last for a half a day at a time and the last one

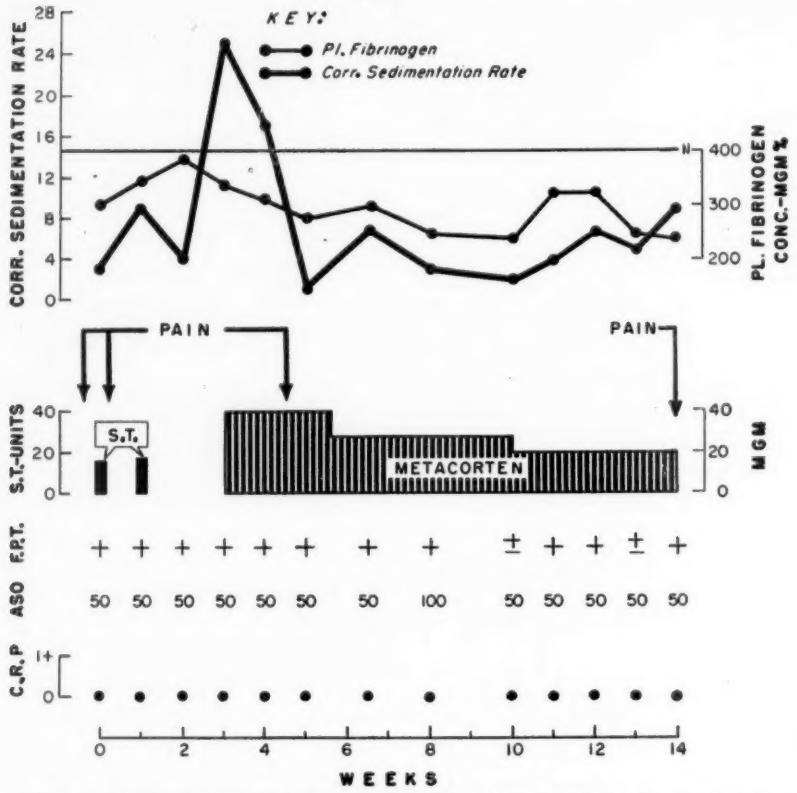


Fig. 3. Graph demonstrating the correlation of the F.P. test, the acute phase reactants and the serum GO-transaminase (S.T.) with the chest pain and therapy used in a patient (A. Z.) with acute idiopathic pericarditis resembling initially acute myocardial infarction.

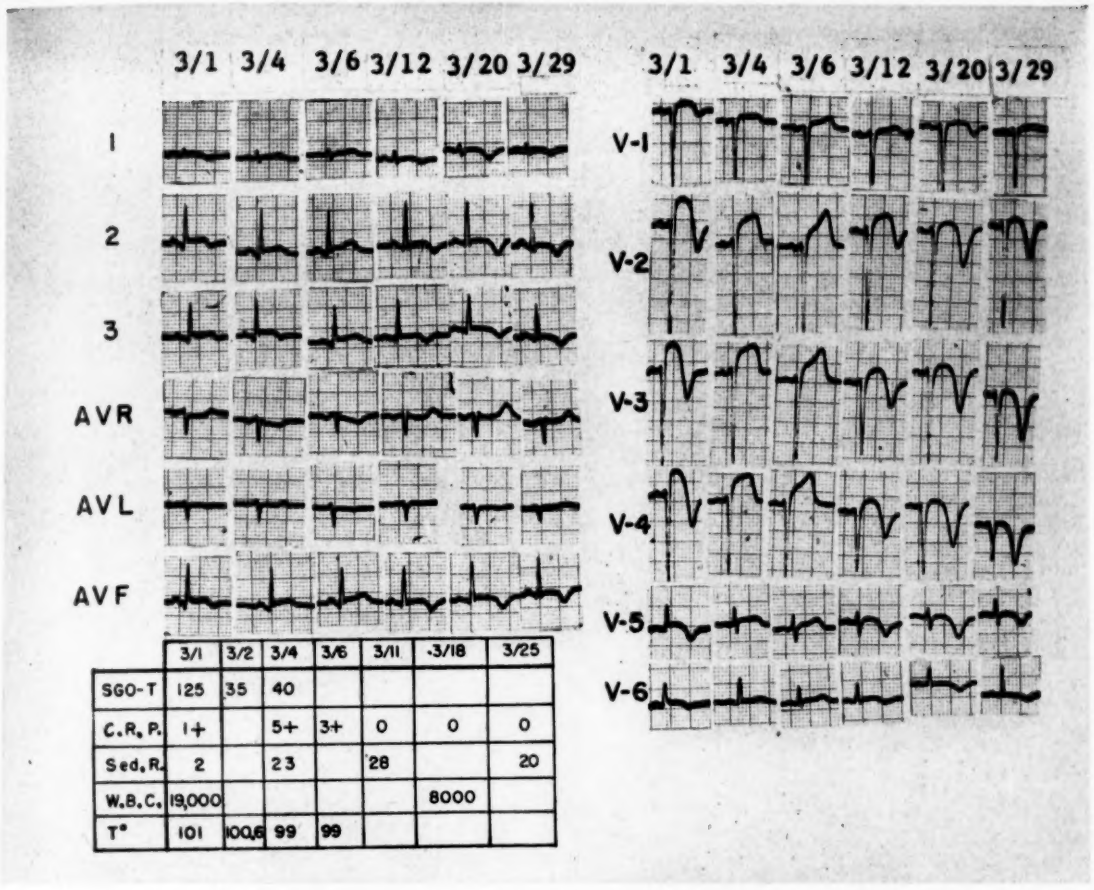
occurred two weeks prior to admission. Past history revealed no relevant data. The family history revealed a significant incidence of premature coronary disease. Physical examination elicited only these positive findings, a slight elevation of temperature and a grade 1 apical systolic murmur. The laboratory tests revealed a normal urinalysis, blood count, and total cholesterol (190 mg/100 ml). Both chest x-ray and ballistocardiogram were normal. Early serial ECGs showed only elevated ST segments consistent with acute pericarditis. The normal SGO-transaminase did not rule out an infarction of limited extent. On the other hand, the positive F.P. test suggested pericarditis. The patient continued to have intermittent though mild chest pain and low grade fever which did not respond to salicylates but responded promptly to steroid therapy. However, the long persistence of a positive F.P. test in spite of this regimen presaged accurately the eventual recurrence of symptoms when steroid dosage was reduced. This relapse was brought under control again by increased steroid dosage.

COMMENT

The clinical course of this patient and the behavior of the acute phase reactants and of the F.P. test were quite in keeping with our observations in other cases of idiopathic pericarditis. It should also be noted that an exercise electrocardiogram done late in the convalescence period after his electrocardiogram had reverted completely to normal did not change after double 2-step exercise.

These observations demonstrate that the determination of the F.P. test, in addition to that of the serum enzymes, GO-transaminase or aldolase, may be of considerable help for the differential diagnosis of acute pericarditis from acute myocardial infarction.

Table I illustrates the differential diagnostic value of these procedures in patients who present themselves with chest pain compatible with either infarction or pericarditis and in whom the ECG is of no diagnostic help. During the acute phase of infarction elevated enzyme levels associated with a negative F.P. test suggest strongly acute coronary occlusion in the absence



	3/1	3/2	3/4	3/6	3/11	3/18	3/25
SGO-T	125	35	40				
C.R.P.	1+		5+	3+	0	0	0
Sed.R.	2		23		28		20
W.B.C.	19,000					8000	
T°	101	100.6	99	99			

Fig. 4. Graph demonstrates temporary normalization of T waves in a patient (W. M.) with acute myocardial infarction. Pericarditis suspected. Nonspecific acute phase reactants consistent with either diagnosis. Serum transaminase ruled out pericarditis (see text).

TABLE I

The Differential Diagnostic Value of the F.P. Test and the Serum Enzyme Level in Myocardial Infarction and Pericarditis

	Acute		Subacute	
	Infarction	Pericarditis	Infarction	Pericarditis
F.P.T.	Negative	Positive	Negative	Positive
S. Enz.	Elevated	Normal	Normal	Normal

F.P.T. = Fibrinogen polymerization test. S. Enz. = Serum enzyme level (SGO-transaminase or aldolase).

of hepatic disease. On the other hand, normal serum enzyme levels and a positive F.P. test suggest acute pericarditis. During the subacute phase the serum enzymes are of little help but a positive F.P. test usually will be obtained in pericarditis if chest pain and/or electrocardiographic changes are still present (Fig. 4).

The occurrence of a type of pericarditis resembling in many respects nonspecific pericarditis has been observed recently by Dressler[20] following myocardial infarction and called the postinfarction syndrome. It appeared of considerable interest to note whether or not the F.P. test would give results in this condition similar to those obtained in nonspecific pericarditis. It has, however, not been possible to carry out the F.P. test in the cases of postinfarction syndrome we have encountered because of the anticoagulation therapy in use. This tends to prolong the procedure beyond practical limits of time.

Summary

(1) The present report concerns itself with comparative studies of the fibrinogen polymerization test, and several acute phase reactants such as the CRP, ESR, and plasma fibrinogen concentration, and also the ASO titer. These were followed serially in patients with idiopathic, rheumatic and presumably tuberculous pericarditis and also in cases of atypical myocardial infarction.

(2) A consistently positive F.P. test indicated the presence, and mirrored the course, of rheumatic and idiopathic pericarditis, while it was negative in tuberculous pericarditis. Of the acute phase reactants only the ESR was abnormal to a comparable degree in all conditions studied. It seems, therefore, that the F.P. test can serve as a valuable aid in the diagnosis of idiopathic pericarditis.

(3) In contrast to all nonspecific acute phase reactants the F.P. test appears not to be suppressed by salicylates or steroid therapy but reflects the activity of the disease and thus provides a useful criterion for the efficacy of therapy.

(4) The F.P. test appears, furthermore, of value for the differential diagnosis between atypical myocardial infarction and acute nonspecific pericarditis, particularly, when used concomitantly with the SGO-transaminase or serum aldolase tests.

Addendum

The procedure used for the F.P. test is a modification of the method originally reported by Losner and Volk.[7,8]

Approximately 15 ml of blood obtained by rapid and meticulous venipuncture are placed into a clean and large test tube. Two graduated centrifuge tubes are prepared in advance by adding to each 0.2 ml of a heparin solution containing 40 mcg per ml of saline. Aliquots of 3 ml of blood are transferred into these two tubes and then placed in a water bath at 37° C. Particular emphasis must be placed upon the very rapid completion of the initial steps including the immediate placement of the heparinized tubes into the water bath.

The blood is allowed to coagulate in the graduated centrifuge tubes. Exactly two hours after clotting the entire coagulum is loosened with a clean applicator and 0.3 ml of 0.1 M sodium citrate is introduced into each tube for determination of fibrinogen by the clot density method in duplicate. Following centrifugation at high speed for 3 min 0.1 ml of supernatant "serum" and 0.1 ml of Difco thromboplastin is again incubated in a microcuvette at 37° C for 3 min and is then placed into the microadapter of a Coleman Spectrophotometer Junior Model 6A. An aliquot of 0.1 ml of 0.02 M $CaCl_2$ is swiftly blown into the microcuvette at which moment a stopwatch is clicked. The galvanometer light beam is then observed closely after it has come to a standstill. Whenever sufficient fibrinogen is present it begins to swing to the left at about 11 to 13 sec after the addition of calcium, thus indicating clotting of the supernatant "serum." This result is designated as a "negative" fibrinogen polymerization test. In the absence of coagulation, however, the galvanometer light beam remains stationary. This in turn indicates absence of fibrinogen in the supernatant "serum" which is attributed to accelerated fibrinogen polymerization. This result is termed a "positive" fibrinogen polymerization test. A limited movement of the galvanometer light beam to the left upon addition of calcium and occurring only at about 18 to 20 sec indicates the presence of a very small amount of fibrinogen. This is interpreted as a "doubtful" or ± fibrinogen polymerization test.

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Application of the Newer Corticosteroids to Augment Diuresis in Congestive Heart Failure

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THE EARLIEST experiences with the original adrenal steroids—corticotropin, cortisone, and hydrocortisone—established that any of them generally enhances tubular reabsorption of sodium and water and tends to create edema. In accord with Starling's doctrine, the resulting increase of venous pressure can lengthen myocardial fibers and diminish cardiac efficiency; hence these same steroids have rightly been considered hazardous when applied to patients with congestive heart failure. On the other hand, it has long been accepted that all three of them often lead to loss of edema when they are used in the treatment of nephrosis.[1,2] More recently, Schemm and his co-workers[3,4] demonstrated that administration of corticotropin to many cases with intractable cardiac failure similarly effected a beneficial excretion of sodium and water. Because of the well known anti-diuretic potency of ACTH, the results of their pioneer studies in cardiac patients were classed as paradoxical.

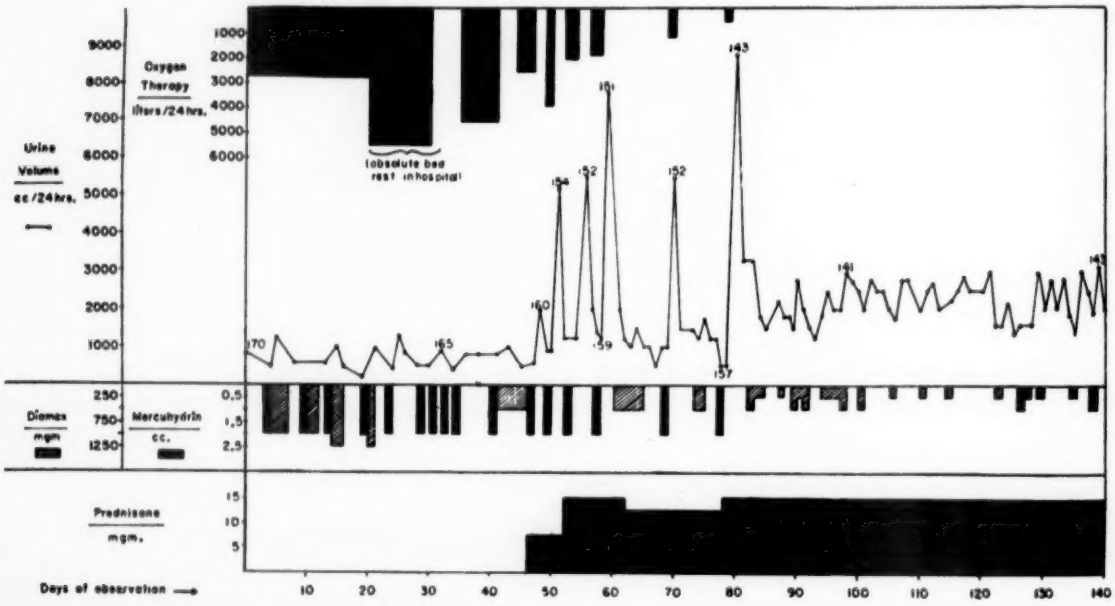

Fig. 1. (From Riemer, A. D.: *Bull. Johns Hopkins Hosp.* 98: 449, 1956). **J. P., male, 47, coronary sclerosis with multiple myocardial infarcts and refractory anasarca. The first day of record was April 1, 1955. The need for oxygen therapy was clinically parallel to the degree of pulmonary vascular congestion. Significant peak body weights are indicated numerically as pounds along the curve of urine volume. Meralluride (mercuhydrin) injections were usually "primed" by ammonium chloride. After prednisone (meticorten), previously ineffective diuretics produced marked losses of water and weight. With 15 mg prednisone daily and sparse doses of acetazolamide (Diamox), compensation was maintained for 13 months. Finally sudden chaotic rhythm and death occurred. Autopsy revealed no evidence of venous congestion or edema.**

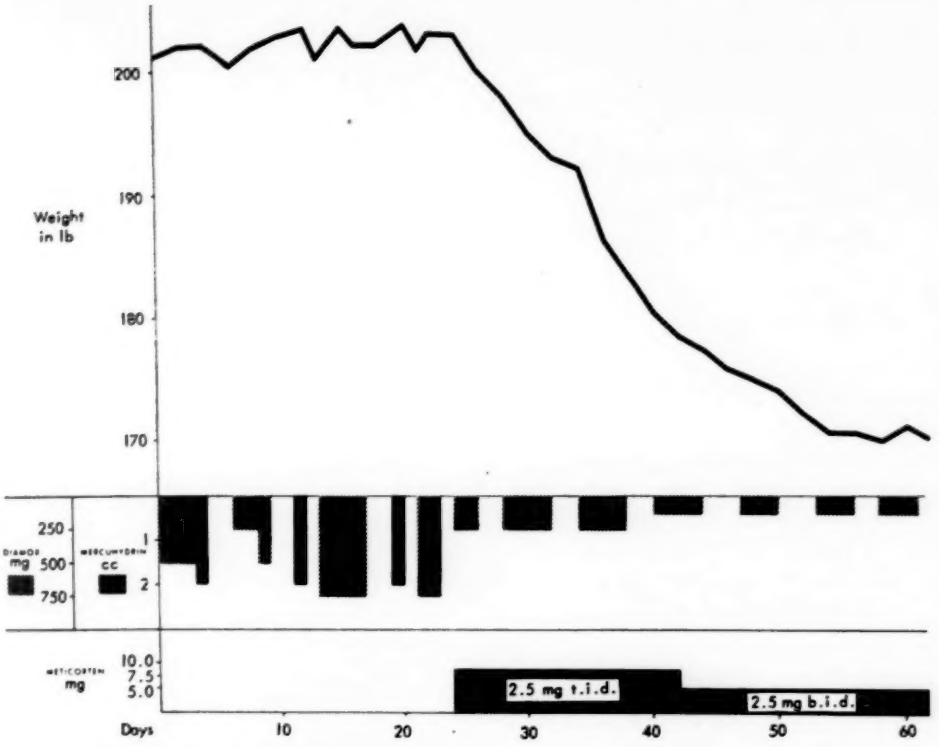

Fig. 2. S. S., female, 71, arteriosclerotic heart disease with refractory anasarca. The first day of record was December 27, 1956. After prednisone (meticorten), there was pronounced restoration of diuretic action by acetazolamide (diamox). Note especially the very small doses of the steroid, the maximum being 7.5 mg/day! By the 203rd day of 5 mg of prednisone/24 hrs and rare small amounts of acetazolamide, complete compensation was being maintained.

Clinical Studies with Prednisone*

Since the development of the relatively "electrolyte-stable" delta-1 derivatives, prednisone and prednisolone, there has been less hesitancy to employ these newer steroids in the presence of edema. Accordingly, many more observations of adrenocorticoid-induced diuresis have been reported. Most notable were the extensive studies of Vesin and Cattan,[5,6] in which prednisone was used as an effective diuretic agent for all forms of edema—whether hepatic, nutritional, renal, or cardiac. Provocative observations pertaining to prednisone-created diuresis in patients with cardiac edema have appeared from several sources. Bickerman *et al.*[7] noted coincidental overcoming of congestive failure in three of a series of cases when the drug was used for the treatment of pulmonary fibrosis. Scalabrino *et al.*[8] found it to produce the same effect in the treatment of Bouillaud's disease (infective endocarditis). Mach *et al.*[9] and Muller *et al.*[10] obtained similar results with prednisone in cardiac patients during the course of their studies on aldosteronism. Bickel[11] reported that it had favorable diuretic action in two cases with refractory cardiac insufficiency.

The following represents a summary of observations from this source, pertaining to prednisone and diuresis as they apply to cases with edema only of cardiac origin. In this series emphasis was placed on those situations for which there was no known indication for use of corticosteroids. Early clinical investigations with the drug, indicated primarily for noncardiac conditions, had revealed significant diuresis in 11 of 13 patients who happened to have co-existing

* The prednisone used in this study was furnished as Meticorten® by Drs. G. Babcock and J. Black, Division of Clinical Research, Schering Corp., Bloomfield, N. J.

TABLE I

Coincidental Diuresis in Prednisone-Treated Patient with Associated Cardiac Edema

Patient	Age	Primary diagnosis	Cardiac diagnosis	Status immediately *before* and 7 days *after* institution of prednisone therapy		
				Meticorten® (mg/24 hr) (for 7 days)	Other corticoids (mg/24 hr)	
					Before	After
M. H.	32	Rheumatic fever	Rheumatic carditis, acute, active	25	—	—
R. G.	19	Disseminated lupus	Pericarditis; myocarditis (lupus)	75	Hydrocortisone, 90	0
G. B.	65	Rheumatoid arthritis	Hypertensive heart disease	15	—	—
F. E.	76	Rheumatoid arthritis	Arteriosclerotic heart disease	20	—	—
A. T.	73	Rheumatoid arthritis	Arteriosclerotic heart disease; hypertensive heart disease	15	—	—
M. M.	58	Status asthmaticus	Cor pulmonale; hypertensive heart disease	40	—	—
J. N.	79	Silicosis; pernicious anemia	Cor pulmonale; arteriosclerotic heart disease	35	—	—
L. C.	44	Lymphatic leukemia and/or lymphosarcoma	Myocarditis, lymphosarcomatous or nonspecific	60	Cortisone, 145	0
A. S.	55	Reticulum-cell sarcomata	Myocarditis, tumorous or nonspecific	70	—	—
C. J.	68	Exfoliative dermatitis	Hypertensive heart disease	20	—	—
E. J.	53	Scleroderma	Myocarditis, sclerodermatous	40	—	—
J. M.	34	Cirrhosis, alcoholic	Beri-beri heart disease	40	—	—
H. G.	56	Pemphigus	Hypertensive heart disease; acute coronary thrombosis with infarction	20	Cortisone, 62.5	0

heart disease with edema. The diuretic effect occurred within four to seven days after beginning the new therapy.[12] (See Table I.)

As a result of those findings, the apparently non-indicated drug was eventually added to the intensive, but no longer effective, therapy of a "terminal" patient who had developed extremely resistant anasarca after multiple myocardial infarctions. There followed an immediate restoration of response to diuretic drugs, conforming with the experiences of Schemm *et al.* with ACTH[3,4] and of Bickel with prednisone.[11] The result was rapid loss of edema and full restoration of compensation.[13] (See Figure 1.) This was maintained for 13 months despite diminished intensity of all other cardiac therapy. Finally he developed sudden chaotic rhythm and quickly expired. Autopsy revealed no evidence of venous congestion or edema.

Since then prednisone has been added to the treatment of resistant cardiac edema in eight additional patients who also had no established need for corticosteroids. All of them had had pro-

TABLE I (Continued)

Coincidental Diuresis in Prednisone-Treated Patient with Associated Cardiac Edema

Status immediately *before* and 7 days *after* institution of prednisone therapy

Cardiac drugs		Edema*		Weight change (pounds) (after 7 days)	Functional† classification		Patient
Before	After	Before	After		Before	After	
—	—	Peripheral, Pulmonary	0	−6	IV	III	M. H.
Diamox®, 750 mg/week	0	Peripheral,* Pulmonary	0	−5	III	I	R. G.
—	—	Peripheral, Pulmonary	Peripheral, Pulmonary	0	II	II	G. B.
Neohydrin®, tabs/week	0	Peripheral,* Pulmonary	Peripheral	−5	III	I	F. E.
—	—	Peripheral	Peripheral	0	II	II	A. T.
—	—	Peripheral, Pulmonary*	0	−3	III	I	M. M.
—	—	Peripheral,* Pulmonary*	0	−6	IV	I	J. N.
Digoxin®, 0.5 mg/day	Digoxin, 0.5 mg/day	Peripheral,* Pulmonary*	Peripheral	−11	IV	II	L. C.
—	—	Peripheral*	0	−3	III	II	A. S.
Diamox, 500 mg/week	0	Pulmonary	0	−3	II	I	C. J.
—	—	Peripheral,* Pulmonary	Peripheral	−7	III	I	E. J.
—	—	Peripheral,* Pulmonary	0	−4	IV	I	J. M.
—	—	Pulmonary	0	−8	IV	III	H. G.

* Indicates "moderate" to "severe" edema; where no asterisk edema was slight.
† Functional classification of heart disease, New York Heart Association.

longed but eventually ineffective treatment with digitalis and diuretic drugs. Electrolyte balance studies had been made in six of the nine patients, but showed no correlation with the degrees of edema; in fact, only two had definite imbalance in the form of hypochloremia, but correction to normal values did not result in improvement of clinical status. After addition of the steroid, seven of the nine experienced prompt diuresis and improvement of cardiac function. None of these had developed glycosuria to aid increase of water output. Two obtained no clinical benefits.[14] (See Table II and Fig. 2.) Especially important was the *continued use of diuretics* and the employment of *very small doses of prednisone*. In the seven successful cases, the efficacy of mercurials or acetazolamide was so intensified that the use of either was followed by marked diuresis on the first day of the new program. This was in contrast to the early series summarized in Table I, wherein larger doses of prednisone alone had resulted in a diuretic effect which was slightly delayed.

Similar augmentation of diuresis followed the

TABLE II

Effects of Prednisone Used Specifically to Aid Diuresis in Cases with Resistant Cardiac Edema

Patient	Age	Cardiac diagnosis	Results *before* and *after* addition of prednisone to diuretic drugs					
			Days of observation*	Meticorten®† (mg/24 hr)	Maximum urine volume (cc/24 hr)			
					Mercuhydrin®		Diamox®	
					Before	After	Before	After
J. P.	47	Multiple myocardial infarcts	44	7.5–15	640 (2 cc I.V.)	8,600 (2 cc I.M.)	800 (500 mg)	2,800 (250 mg)
S. S.	71	Arteriosclerotic heart disease with hypertension	30	7.5–5	400 (2 cc I.V.)	—	320 (750 mg)	3,600 (250 mg)
T. M.	83	Old anterior and acute posterior myocardial infarcts	6	7.5–20	280 (2 cc I.V.)	690 (2 cc I.V.)	—	—
N. D.	61	Arteriosclerotic heart disease	60	15	580 (2 cc I.M.)	2,100 (½ cc I.M.)	400 (750 mg)	800 (125 mg)
D. W.	76	Arteriosclerotic heart disease	38	10	710 (2 cc I.M.)	—	450	1,200
N. W.	52	Arteriosclerotic heart disease with hypertension	32	10–17.5	1,150 (2½ cc I.M.)	Not recorded (1 cc I.M.)	(500 mg) —	(125 mg) —
I. H.	56	Arteriosclerotic heart disease	22	12.5	520 (1 cc I.M.)	1,600 (1 cc I.M.)	—	—
D. R.	49	Hypertensive heart disease	14	7.5–20	870 (2 cc I.V.)	1,220 (2 cc I.V.)	600 (500 mg)	Not recorded (250 mg)
S. R.	70	Arteriosclerotic heart disease	54	10	800 (2 cc I.V.)	1,100 (½ cc I.M.)	—	—

* Limited to include time of *maximum* diuretic effect.

† There was no previous therapy with "sodium-retaining" steroids in this series.

use of prednisone in six patients with decompensated rheumatic heart disease and in three patients with decompensated asthmatic cor pulmonale. Although this effect may have been largely attributable to specific anti-inflammatory action by the indicated steroids, just as it may have been in the patients listed in Table I and in the other early reports,[5–11] it is here briefly mentioned to permit consideration of the possible practical value of corticosteroids in just such frequently encountered situations.

Newer derivatives of prednisolone reveal, in addition to increased biologic potency, probable promise for similar beneficial diuresis in cases with edema. In animal experiments it has been shown that hydroxylation at the 16-alpha position of delta-1 hydrocortisone abolishes the marked sodium retaining activity of 9-alpha-fluoro-steroids.[15] This led to the synthesis of a compound called triamcinilone, which produces a very significant urinary excretion of sodium and water.[16] Similar natriuresis and water diuresis follow administration of 6-methyl prednisolone.[17] Sufficient clinical data with the use of these derivatives are not yet available.

Discussion

There are many possible mechanisms underlying the well documented diuretic effects which followed administration of adrenal corticosteroids. Some of the generally less important factors which have been suggested as being contributory or causative are: (a) nonspecific improvement of mentality or appetite,[18] (b) specific anti-inflammatory action by steroids, (c) cor-

TABLE II (Continued)

Effects of Prednisone Used Specifically to Aid Diuresis in Cases with Resistant Cardiac Edema

Results *before* and *after* addition of prednisone to diuretic drugs

Edema		Weight change (pounds)	Functional classification‡		Comments	Patient
Before	After		Before	After		
Pulmonary,* Peripheral*	0	−24	IV	II	Good clinical response; fully compensated for 13 months; finally sudden arrhythmia and death occurred; autopsy revealed no edema	J. P.
Pulmonary,* Peripheral*	Peripheral	−33	IV	I	Good clinical response	S. S.
Pulmonary,* Peripheral	0	Not taken	IV	Patient died	Diminution of all edema but rapid myocardial failure and death occurred. Autopsy revealed cerebral edema only	T. M.
Pulmonary, Peripheral*	0	−24	III	I	Good clinical response	N. D.
Pulmonary,* Peripheral	0	−14	III	I	Good clinical response	D. W.
Pulmonary,* Peripheral	Pulmonary	−15	III	II	Good clinical response	N. W.
Pulmonary	0	−5	III	I	Good clinical response	I. H.
Pulmonary, Peripheral	Pulmonary, Peripheral	−1	III	III	Slight increase of diuresis observed. Response not significant clinically	D. R.
Peripheral*	Peripheral	−9	III	II	Good clinical response	S. R.

* Indicates "moderate" to "severe" edema; where no asterisk edema was slight.
‡ Functional classification of heart disease, New York Heart Association.

ticogenic hypothyroidism with its attendant decrease of metabolic work-load,[19] (d) increased mobilization of glucose for muscle energy,[20]—particularly as it pertains to the myocardium, (e) increased alveolar transport of oxygen, resulting in diminished hypoxia,[7] and (f) stimulation of erythropoiesis when anemia exists.[21]

In general, these factors appear to play minor roles in the edematous patients who have cardiac disease as a single or primary entity. In the present series, diuresis was immediate after adding very small doses of the steroids to the diuretic drugs; therefore, there was virtually no opportunity for the development of nonspecific euphoria, of specific anti-inflammatory effects, and especially of corticogenic hypometabolism. Also, clinical evidence of improved myocardial function first appeared *after* there had been substantial losses of water; this suggests that gluconeogenesis for better heart muscle contraction is less likely a primary factor than the reduction of hypervolemia. Also, there was good response in patients who had predominantly peripheral edema with no clinical evidence of hypoxia from impaired oxygen transport at the pulmonary alveolar level. Finally, only one of the patients had significant anemia.

Physiologic Mechanisms of Steroid-Induced Diuresis: More intimately related to the observed induction of renal water loss are several pertinent physiologic facts about the adrenal steroids. They may: (a) increase glomerular filtration rate,[22] (b) preserve protein-oncotic pressure[23] especially as applied to the glomerular capillaries, (c) contain a "sodium-diuretic fac-

tor,"[24] (d) inhibit anti-diuretic hormone,[25] (e) re-establish effectiveness of diuretic drugs,[3,11,13] and (f) they seem to counteract the sodium reabsorbing function of aldosterone.[13,26] Although most of these mechanisms are interdependent, the relative importance of each will be considered individually.

Studies suggest that the augmented glomerular filtration plays a major role only when the edema be severe, and that it is usually quantitatively less important than diminished tubular absorption of sodium.[22] Preservation of capillary integrity and its consequent retention of intravascular protein has been demonstrated in animal experiments;[23] proper evaluation of this finding requires clinical studies in humans Likewise, the significance of the "sodium-diuretic factor," obtained from the urine of ACTH-treated nephrotics,[24] needs more clinical appraisal. The inhibition of neuro-hypophyseal anti-diuretic hormone, permitting loss of water, is generally accepted as a transient or occasional phenomenon; it is stated that sustained release of the hormone occurs only in patients with extreme edema.[28] The resorted effectiveness of diuretic drugs has been repeatedly demonstrated,[3,11,13] and the present investigation in particular indicates that it can be a very important factor. The mechanism for this is not yet understood.

Edema and Aldosterone: The hypothesis of suppressed aldosterone activity is especially intriguing. Many established facts about this steroid may be integrated to offer some possible explanations for the observations under discussion. Evidence is accumulating that increases of edema are closely correlated with increased amounts of aldosterone, which is the most potent sodium-retaining hormone secreted by the adrenals. This has been demonstrated by the creation of swelling following administration of the steroid,[29] and conversely by heavy excretion of ascitic fluid after total adrenalectomy[30] or after administration of amphenone.[31] There is the possibility that a high level of "secondary aldosterone" might occasionally be due to impaired degradation of the hormone in a congested liver.[32] The absence of edema in Conn's dramatic case of "primary aldosteronism" with a tumor secreting large amounts of the substance,[33] may be partly explained by shift of the retained sodium into the cells to replace the heavy losses of potassium, thereby diminishing the volume of extracellular fluid.

On the other hand, there have been many examples of the tendency of other adrenal steroids to diminish or counteract the mineralocorticoid antidiuretic activity of aldosterone. Desoxycorticosterone, in doses proven to cause sodium retention equal to that of aldosterone, permits more urinary excretion of water than the latter.[34] When there is hypersecretion of other steroids by the adrenal cortex, such as in Cushing's disease, administration of aldosterone is not likely to cause sodium retention.[35] Likewise, in patients with congenital adrenal hyperplasia there is often a salt-losing tendency which resists correction by administration of aldosterone.[36] Even Conn's nonedematous case of "primary aldosteronism" developed marked urinary excretion of the retained sodium when given ACTH or cortisone.[32] Insofar as the pituitary has little influence on aldosterone secretion, the occasionally observed effectiveness of ACTH in that direction might be secondarily due to its tropic production of hydrocortisone.

Similarly, in Addison's disease, the maintenance of electrolyte equilibrium by aldosterone or by desoxycorticosterone is altered when the treatment is changed to cortisone or hydrocortisone, the result being marked loss of sodium and water.[35] In the same manner, many patients whose treatment had been changed from cortisone to prednisone, experienced loss of the previous drug-induced edema.[37–39]

Analysis of the above data suggests the concept that the ability of an adrenal steroid to antagonize aldosterone may be inversely proportionate to the degree of its sodium retaining potency. Soffer would correlate the diuretic activity by a steroid with the degree of its capability to induce expansion of extra-cellular fluid volume.[40] Forsham postulates that there is competition for sodium reabsorption by the different steroids directly at the renal tubular level.[40] Whatever be the basis, there appears to exist a counter-acting effect by adrenal corticosteroids on the "secondary aldosteronism" of cases with cardiac edema.

Summary and Conclusions

The potentiality of adrenal steroids for aiding diuresis in congestive heart failure has been repeatedly documented. Several mechanisms seem to be involved, and the role of each has not yet been fully evaluated. Most important appear to be the inter-related actions which alter physico-chemical activities in the nephron, especially the re-potentiation of diuretic drugs and possibly the suppression of "secondary aldosteronism." This specific diuretic function may be additive to the anti-inflammatory action by steroids in situations such as decompensated rheumatic heart disease or decompensated cor pulmonale of pulmonary fibrosis.

Routine use of adrenal steroids in the therapy of cardiac edema is not now being advocated. Especially for resistant congestive heart failure one must first try standard measures—particularly the use of digitalis, proper administration of diuretic drugs, and correction of electrolyte imbalance. When these methods eventually fail, as they do in many cases, the addition of corticosteroids may be considered. If that decision be made, there must be the usual precautions regarding associated disorders such as peptic ulcer, tuberculosis, and infections in general. If used, it is urged that all basic cardiac therapy be continued, especially the administration of diuretic drugs which may become immediately effective. Also, with diuretics, the dose of the steroid might be very small and well below the "critical level" for salt retention, which is known to exist even with the new "electrolyte-stable" compounds.

For clinical application, there are as yet no established pharmaceutical standards for dosage, time of day, and duration of administering the corticosteroids. Also, the treatment is occasionally unsuccessful, and attempted explanations for this are not yet conclusive. It is evident that there is a need for extensive physiological and clinical investigation of this newly suggested adjunct to the therapy of congestive heart failure.

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Addendum

Since submitting this manuscript on September 21, 1957 many confirmatory case reports from several centers have been published. Also, provocative observations have been made pertaining to (1) prednisone potentiation of diuresis by chlorothiazide (Diuril® Merck), and (2) successful attainment of sodium and water loss by employment of steroidal antagonists of aldosterone, SC-5233 and SC-8109 (Searle), (Liddle, G. W.: *Science*, 126: 1016, 1957).

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Experimental Studies

Laboratory and Clinical Observations on Ethoxzolamide (Cardrase) as a Diuretic Agent*

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CARBONIC anhydrase inhibitors have come into widespread use over the past five years as oral diuretics. However, because of limited potency and the development of tolerance, currently available carbonic anhydrase inhibitors are of limited value. Therefore, further research is being conducted in an attempt to find more effective diuretic agents of this type. The following report presents some laboratory and clinical observations on ethoxzolamide (Cardrase®)‡ (U-4191), a carbonic anhydrase inhibitor of the sulfonamide type (Fig. 1).

STRUCTURAL FORMULAE

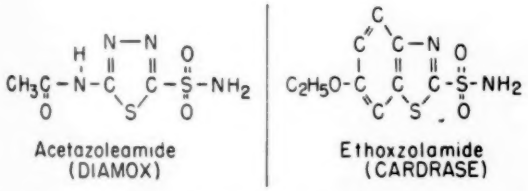

Fig. 1. Structural formulae of ethoxzolamide (cardrase) and acetazoleamide (diamox).

METHODS AND MATERIALS

Observations were made on two groups of patients. Group I consisted of 10 patients in mild heart failure on whom diuretic bioassay studies were carried out. Dose range studies were done on six of these patients. Group II consisted of 13 outclinic patients with moderately severe heart failure on whom chronic toxicity and drug tolerability studies were done.

The bioassay studies were conducted in a metabolic ward using men with mild heart failure who had previously demonstrated evidence of edema but who at the time of the study were edema-free. Cardrase (ethoxzolamide) (U-4191) was given to ten patients for two successive days. They drank 3,000 ml of distilled water per 24 hours and consumed a diet containing 50 meq of sodium per 24 hours. Twenty-four-hour urine specimens were collected and analyzed for sodium, potassium, chloride, and volume. The patients were weighed each morning before breakfast and after voiding. After suitable control periods, the patient's urinary excretion rate of sodium was approximately 90 to 95 per cent of the dietary sodium intake. The patient's excretion rate of sodium continued at this constant level for at least three days (Fig. 2). The patient was then given a single dose of the experimental drug after breakfast for two consecutive days and the body weight and excretion rates of water and electrolytes were determined. After the drug was stopped, the pa-

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Supported in part by a grant from the Houston Heart Association.

† Present address.

‡ Upjohn and Co.

tient's excretion rate of sodium usually decreased for one to three days during which time the body stores of sodium were replenished and the patient once more began to excrete at a fairly constant rate (Fig. 2) which was very close to his

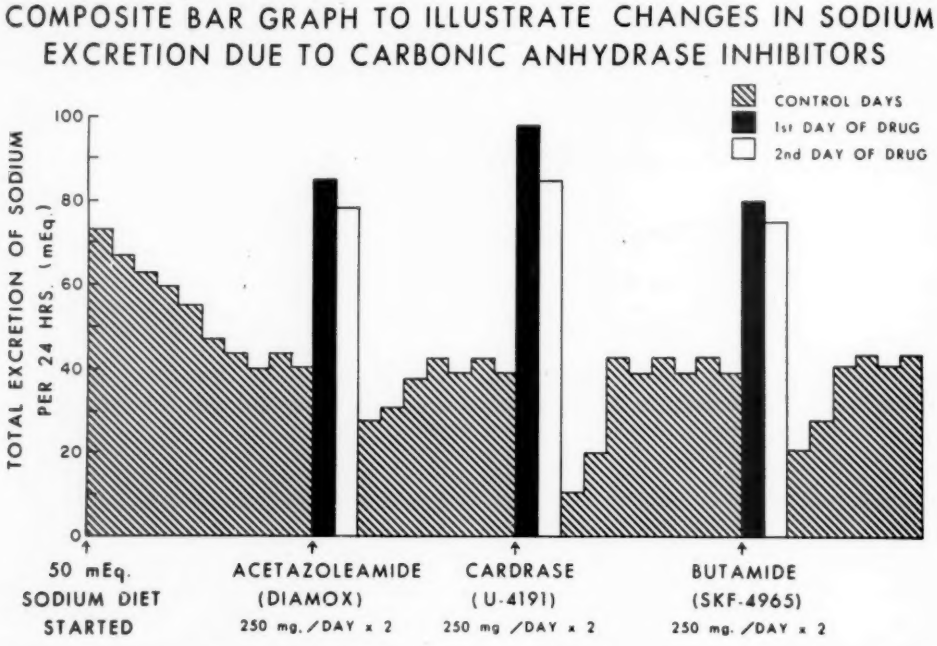

COMPOSITE BAR GRAPH TO ILLUSTRATE CHANGES IN SODIUM EXCRETION DUE TO CARBONIC ANHYDRASE INHIBITORS
CONTROL DAYS
1st DAY OF DRUG
2nd DAY OF DRUG
TOTAL EXCRETION OF SODIUM PER 24 HRS. (mEq.)
100
80
60
40
20
0
50 mEq. SODIUM DIET STARTED
ACETAZOLEAMIDE (DIAMOX) 250 mg./DAY x 2
CARDRASE (U-4191) 250 mg /DAY x 2
BUTAMIDE (SKF-4965) 250 mg. /DAY x 2

Fig. 2. Bar graph showing changes in sodium excretion that occur during equilibration and following the administration of carbonic anhydrase inhibitors.

dietary sodium intake. Thus, usually seven days elapsed between the administration of successive doses of the drug to each patient.

The range between threshold doses and maximum effective doses (for increasing water and electrolyte excretion with cardrase) was quite variable from patient to patient. The minimum dose administered was 31.75 mg. The maximum dose used was 500 mg given as a single dose in the morning. It was possible to increase the dose in an incremental fashion in each patient (group I) until further increases in dosages did not produce a significantly greater increase in the excretion of sodium. This point was arbitrarily termed the "apex" point. This same procedure has been used to establish the apex point for other carbonic anhydrase inhibitors.[1] After the dose was established which produced maximum natriuresis in the majority of the patients, a dose of at least two times this dose at the apex was administered as the comparative testing dose of the drug for the bioassay studies. The response was then compared to that obtained with Diamox®. Thus, the test dose of diamox was 250 mg daily and the dose of cardrase was also found to be 250 mg daily.

Group II consisted of 13 ambulatory clinic patients in various degrees of cardiac failure. According to the functional classification of the American Heart Association, six were Class II, six were Class III and one was Class IV. The etiology of the heart disease was arteriosclerotic heart disease in five patients, syphilitic heart disease in two patients, hypertensive heart disease in five patients and rheumatic heart disease in one patient. Prior to the current study, all of the patients were receiving either Mercuhydrin® given parenterally or Neohydrin® given orally. All of the patients were receiving digitalis. The diuretics were discontinued but the patients continued to receive digitalis. The age range in this group was 48 to 73 years with an average age of 59 years. Ten patients were male and three were female. Eleven of these patients were Negroes and two were white.

After being deemed suitable for observations, all patients in group II were given 500 mg of

cardrase daily in two divided doses for five consecutive days out of each week. The patients returned semi-weekly for evaluation while receiving this dose. On the 14th day the dosage was increased to 1,000 mg daily in four divided doses administered for an additional two weeks. The patients were seen for evaluation at least semi-weekly while receiving the high dose. As an aid to evaluation in those patients who developed severe side effects, the drug was discontinued and a placebo substituted without the patient's knowledge.

Results

BIOASSAY

The dose range data for cardrase (ethoxzolamide) are tabulated in Table I which includes the observations of the responses to doses ranging from 31.75 mg to 500 mg in six patients. It is obvious that there was no greater increase in water or sodium excretion with the larger 500 mg dose than there was following a dose of 250 mg ($p > 0.10$). In fact, five out of six patients showed no greater increase in sodium excretion with a dose of 500 mg than they did with the 125 mg dose. The dose of 31.75 mg showed a minimal increase in sodium excretion (Table I) without an increase in water excretion, whereas the 62.5 mg dose showed a definite and consistent natriuretic response. The observations also indicate that when the drug was given for two successive days, the increase in water and sodium excretion was significantly less on the second day than on the first, suggesting that tolerance develops rapidly.

Table II summarizes the observations made on ten patients using a dose of cardrase of 250 mg as a comparative bioassay study. The values are recorded as the responses of sodium, potassium, chloride, and water excretion and decrease in weight as an average of two consecutive days during which the comparative test dose was administered.

The diuretic response to cardrase indicates an average increase in sodium excretion of 44 meq/day ($p < 0.001$). Concurrently, there was an increase in potassium excretion of 37 meq ($p < 0.001$). There was a slight reduction in chloride excretion which was not statistically significant ($p < 0.10$). The increase in water excretion, however, was significant ($p < 0.01$). Weight changes paralleled the increase in water excretion ($p < 0.01$).

The response to diamox (acetazoleamide) was very similar to the response to cardrase. Sodium excretion increased 35 meq ($p < 0.001$) and potassium excretion increased 36 meq ($p < 0.001$) whereas chloride excretion decreased ($p < 0.01$). There was a highly significant increase in water excretion ($p < 0.001$) but the weight loss was barely significant ($p < 0.02$).

ACUTE TOXICITY (GROUP I)

Only two patients out of ten experienced side effects with the administration of 250 mg of cardrase a day for two days. One of the patients complained of paresthesias about the mouth, weakness, and lethargy and the other complained of weakness and lethargy. Side effects were not observed when a dose of 125 mg was given to six patients for two days.

CHRONIC TOXICITY (GROUP II)

Eleven patients in group II completed a full 14 days on cardrase receiving the 500 mg dose. One patient discontinued the drug after seven days because of diarrhea, paresthesias, fatigue and weakness, and leg cramps and the other patient discontinued the drug because of abdominal cramps and diarrhea. The common side effects on the 500 mg dose were: lethargy and weakness in eight patients, paresthesias in two patients, anorexia in three patients, intestinal cramps and diarrhea in six patients, and dizziness in two patients.

The incidence of side effects did not increase when the dose of cardrase was increased to 1,000 mg daily but the severity increased significantly. Partial to complete tolerance developed to the common side effects in approximately half of the patients in group II in whom drug administration was continued. These observations indicate that the side effects are prohibitive when doses of cardrase of 500 mg or more are used. Since the bioassay studies indicate that the diuretic response to 500 mg is no more than the response to 250 mg doses and very little greater than doses of 125 mg, probable doses in excess of 125 mg per day should not be

employed and certainly doses in excess of 250 mg should not be used for therapeutic purposes.

Observations on therapeutic effectiveness in the outpatients indicated that only six patients (46 per cent) were maintained as well with the diuretic, cardrase, administered for five days out of each week as they were on their previous mercurial diuretic therapy. Observations on sodium excretion with continuous administration of cardrase indicate why this is so (Fig. 3A) (Table I). When the drug is administered continuously, tolerance develops so that after three days of continuous administration no further diuretic response is obtained (Fig. 3A). Therefore, it becomes necessary to interrupt the cardrase administration every second day if renal responsiveness to the drug is to be regained. Similar observations have been made with diamox (Fig. 3B). Thus, these drugs cannot be administered for more than three or four days out of each week and for no more than two successive days at any one time. This immediately relegates cardrase to the treatment of patients with only mild heart failure or as adjunctive therapy to more potent diuretics. By contrast, organo-mercurial compounds continue to promote natriuresis for prolonged periods of time with continued daily drug administration (Fig. 4).

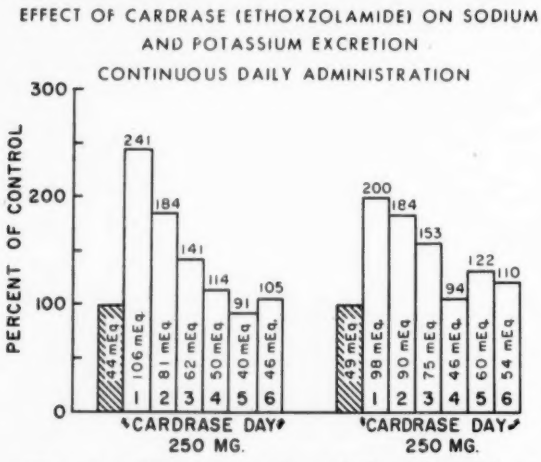


Fig. 3A. Effect of cardrase (ethoxzolamide) on sodium and potassium excretion. After two days of continuous administration most of the natriuretic effect has been lost and it becomes necessary to discontinue administration of the drug for 48 to 72 hr before this natriuretic response to cardrase can again be obtained.

Discussion

The use of carbonic anhydrase inhibitors, as oral diuretics, has found clinical application in the treatment of mild edema due to numerous causes. The mechanism of the diuretic effect is the inhibition of the carbonic anhydrase system at the level of the distal tubule in the kidney. This enzyme system is responsible for the exchange of intracellular hydrogen ions with the intratubular sodium which results in acidification of the urine. Inhibition of this process thus increases the excretion rate of sodium and potassium followed by an obligatory loss of water. Glomerular filtration rate and renal blood flow are not increased.[2] In fact, cardrase produced a slight reduction in glomerular filtration rate

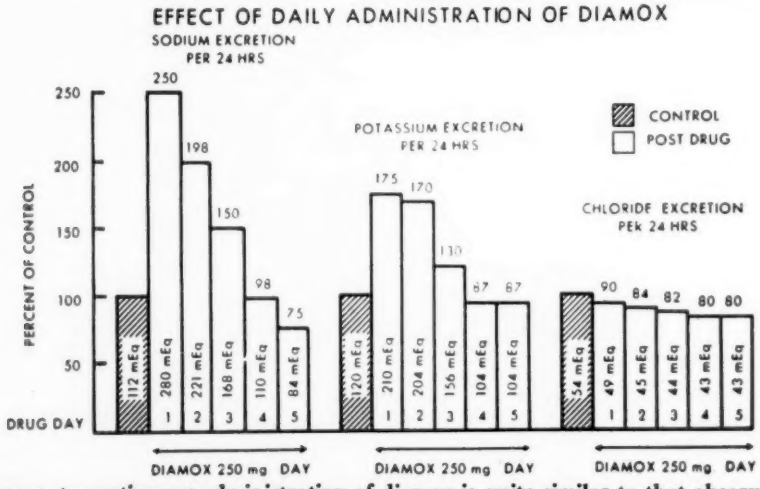


Fig. 3B. The response to continuous administration of diamox is quite similar to that observed with cardrase (Fig. 3A).

TABLE I

Observations of Water and Sodium Excretion Made with Increasing Doses of Cardrase (Ethoxzolamide)

Patient	C	D_1	D_2	$\frac{D_1 + D_2}{2}$	Increase $\left(\frac{D_1 + D_2}{2} - C\right)$	C	D_1	D_2	$\frac{D_1 + D_2}{2}$	Increase $\left(\frac{D_1 + D_2}{2} - C\right)$	C	D_1	D_2	$\frac{D_1 + D_2}{2}$	Increase $\left(\frac{D_1 + D_2}{2} - C\right)$
	Dose of cardrase = 31.75 mg					Dose of cardrase = 62.5 mg									
	Sodium excretion expressed in meq per 24 hr														
1 J. A.	44	52	52	52	8	48	86	76	81	33					
2 W. R.	41	41	47	44	3	49	91	83	87	38					
3 D. V.	57	66	60	63	6	51	76	90	83	32					
4 J. A.	53	64	57	61	8	56	84	86	85	29					
5 D. A.	48	54	50	52	4	47	98	80	89	42					
6 Jac.	50	64	58	61	11	56	78	70	74	18					
Mean	49	57	54	56	7	51	86	81	83	32					
	Dose of cardrase = 125 mg					Dose of cardrase = 250 mg					Dose of cardrase = 500 mg				
	Sodium excretion expressed in meq per 24 hr														
1 J. A.	47	108	81	95	48	45	120	73	97	52	44	122	61	92	48
2 W. R.	41	85	91	88	47	57	118	102	110	53	50	120	71	96	46
3 D. V.	53	96	72	84	31	56	100	63	82	26	53	72	64	68	15
4 J. A.	50	102	85	94	44	47	140	68	104	57	49	147	60	104	55
5 D. A.	45	112	106	109	64	51	161	107	134	83	44	151	73	112	68
6 Jac.	43	72	51	62	19	44	76	43	60	16	51	75	74	75	24
Mean	47	96	81	89	42	50	119	76	98	48	49	115	67	91	43
	Water excretion expressed in l/24 hr														
1 J. A.	3.12	4.10	3.80	3.95	0.83	3.04	3.86	3.30	3.58	0.54	2.98	3.62	3.23	3.43	0.45
2 W. R.	3.56	3.56	3.80	3.68	0.12	3.10	4.10	4.00	4.65	0.95	4.22	4.82	4.40	4.61	0.39
3 D. V.	3.10	3.44	3.33	3.39	0.29	3.64	3.96	3.84	3.90	0.26	3.38	4.10	3.94	4.02	0.64
4 J. A.	2.36	2.72	4.30	3.51	1.15	4.08	4.96	5.10	5.03	0.95	3.72	4.42	4.26	4.34	0.62
5 D. A.	3.89	3.94	4.08	4.01	0.12										
6 Jac.	3.35	4.10	3.22	3.66	0.31	3.10	3.52	3.20	3.36	0.26	2.94	2.98	3.30	3.14	0.20
Mean	3.23	3.64	3.76	3.70	0.47	3.39	4.08	3.98	3.98	0.59	3.45	3.99	3.83	3.91	0.46

Key: C = Control observations.
D_1 = Observations during first day of cardrase administration.
D_2 = Observations during second day of cardrase administration.

which was not observed in the animals which received diamox. Therefore, it appears that the diuretic response is related primarily to the tubular effect of this compound.

When ethoxzolamide (cardrase) is administered to unhydrated dogs there is a significant diuretic response which is similar to the response to diamox.[2] Likewise, a diuretic effect is noted in hydrated dogs which is similar to the response to diamox.

When the diuretic effect of cardrase is compared with diamox (acetazoleamide) clinically (Tables II and III), there appears to be no essential difference between the diuretic potency of these two agents. However, the toxicity studies indicate that the therapeutic-toxic range is

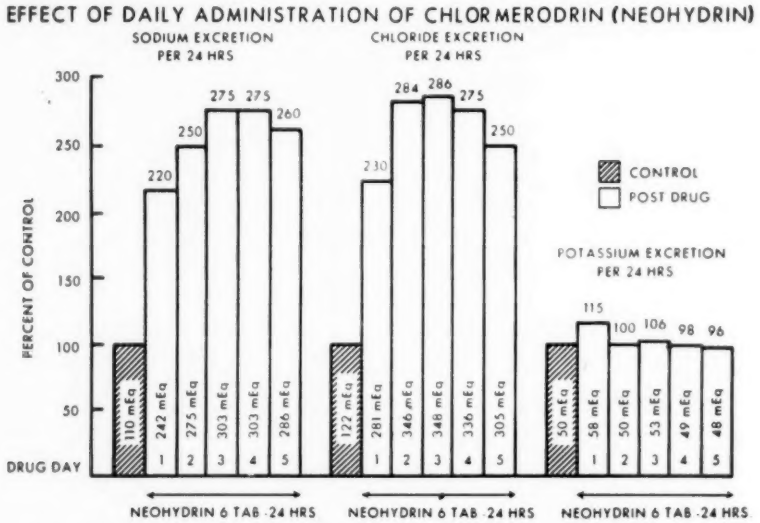

EFFECT OF DAILY ADMINISTRATION OF CHLORMERODRIN (NEOHYDRIN)
SODIUM EXCRETION PER 24 HRS
CHLORIDE EXCRETION PER 24 HRS
POTASSIUM EXCRETION PER 24 HRS
PERCENT OF CONTROL
DRUG DAY
CONTROL
POST DRUG
NEOHYDRIN 6 TAB -24 HRS
NEOHYDRIN 6 TAB -24 HRS
NEOHYDRIN 6 TAB -24 HRS

Fig. 4. Contrasted with Figures 3A and 3B, it is seen that enhancement of sodium excretion is continued and even increased by daily administration of a mercurial diuretic administered orally (neohydrin). The same is true of chloride excretion but potassium excretion is not altered.

TABLE II

The Effect of Cardrase (U-4191) (250 mg) Administration on Body Weight and the Increase in Excretion Rates of Water and Electrolytes

Patient	Change in sodium excretion (meq/24 hr)	Change in potassium excretion (meq/24 hr)	Change in chloride excretion (meq/24 hr)	Change in water excretion (*l*/24 hr)	Weight change (kg)
J. J.	48	44	+ 4	+0.83	+0.30
X. D.	44	16	+ 8	+1.05	−0.30
H. J.	45	20	−19	+0.07	−0.10
J. J.	58	23	− 0	+0.54	−0.70
W. W.	46	53	+ 4	+0.62	−0.80
A. D.	24	38	− 9	−0.05	−0.30
J. J.	52	21	+ 9	−0.08	−1.20
W. W.	51	59	−24	+0.16	−1.00
A. D.	15	42	−14	+0.56	−0.60
H. B.	52	55	−16	+0.63	−1.00
Average	44	37	− 6	+0.43	−0.57
P Value †	<0.001	<0.001	<0.1	<0.01	<0.01

† $t = X\sqrt{\frac{n(n-1)}{S_{x^2}}}$

more narrow for cardrase (Table IV) than it is in the case of diamox.[2-4] Therefore, when using cardrase it is essential that the smallest effective dose be employed. Our data indicates that there is probably no need for using a dose in excess of 125 mg per day (Table I) and certainly not in excess of 250 mg per day. If this dose is not exceeded, the toxic manifestations of cardrase are minimized (Table IV). However, if the dose is in excess of this amount, it can be anticipated that the side effects associated with the administration of cardrase will be considerably higher than in the case of diamox administration (Table IV). The dosage response as to diuretic effect is the same for cardrase as it is for diamox. In contrast, the diuretic response to oral Neohydrin or mercuhydrin given parenterally continues to rise when doses are given which are greater than those generally employed clinically (Fig. 5A and 5B).

TABLE III

The Effect of 250 mg of Acetazoleamide (Diamox) given Orally on Body Weight and Excretion Rates of Water and Electrolytes

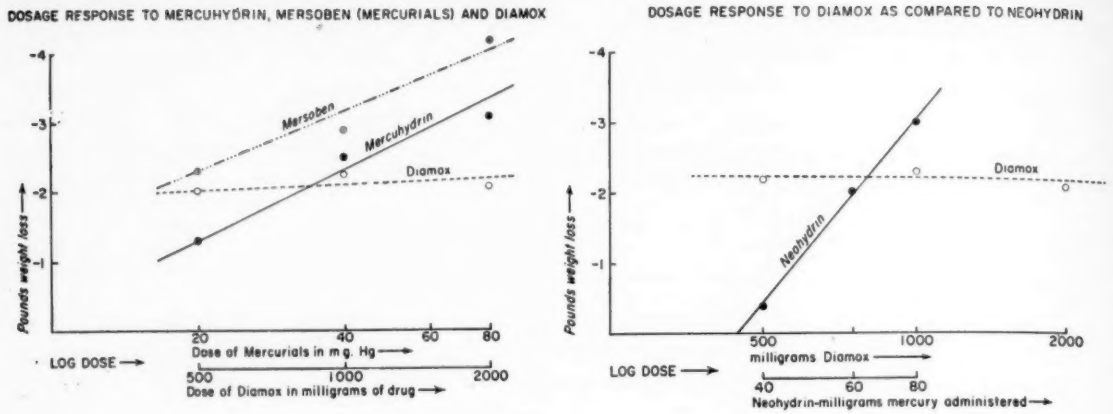
Patient	Increase in sodium excretion meq/24 hr	Increase in potassium excretion meq/24 hr	Decrease in chloride excretion meq/24 hr	Increase in water excretion l/24 hr	Decrease in weight kg
E. G.	30	38	−12	0.61	−0.6
J. W.	26	30	− 1	0.46	−0.2
J. B.	24	15	−12	0.10	0.0
G. G.	30	40	− 4	0.18	−0.4
T. P.	40	30	−18	0.60	−0.6
T. A.	60	42	−12	0.78	−0.1
G. R.	33	50	0	0.42	0.0
S. B.	48	38	− 4	0.24	−0.6
B. B.	40	48	−16	0.72	−0.7
J. H.	20	28	−12	0.24	−0.2
Average	35	36	− 9	0.44	−0.3
P Value	<0.001	<0.001	<0.01	<0.001	<0.02

TABLE IV

Comparison of Common Side Effects of Large and Small Doses of Cardrase Compared to Diamox and Neohydrin

	Cardrase				Diamox 500 mg dose		Neohydrin dose equivalent to 60 mg Hg	
	250 mg dose		500 mg dose					
Number of patients treated	10		13		18		18	
Side effects	Number	%	Number	%	Number	%	Number	%
Diarrhea	—	—	6	46	—	—	4	22
G-I cramps	—	—	4	31	—	—	5	28
Nausea and vomiting	—	—	—	—	1	6	5	28
Weakness and lethargy	2	20	8	62	3	17	4	22
Anorexia	—	—	3	23	2	11	4	22
Paresthesias	1	10	2	15	1	6	—	—
Dizziness	—	—	2	15	—	—	—	–

The indications for the use of carbonic anhydrase inhibitors include maintenance therapy between parenteral mercurial injections for the treatment of severe congestive heart failure, the



A B

Fig. 5A. Increasing doses of mercurial diuretics (mersoben and mercuhydrin) are accompanied by increasing diuresis as manifested by loss in body weight. Increasing the daily dose of the carbonic anhydrase inhibitor diamox above 250 mg does not increase the diuretic response. This is also true of cardrase (Table I). B. The orally administered mercurial diuretic neohydrin also presents a progressive dose-response curve contrasted to an unchanging curve seen with diamox when doses in excess of 500 mg are employed. (Courtesy *J. Chronic Diseases* 2: 670, 1955).

treatment of mild heart failure, premenstrual edema, and numerous other causes of edema secondary to water and sodium retention. These drugs are considerably less potent in promoting sodium and water excretion than are the parenteral mercurial diuretics.

Summary and Conclusions

(1) The diuretic response to a carbonic anhydrase inhibitor, ethoxzolamide (cardrase) (6-ethoxybenzothiazole 2-sulfonamide) has been studied and has been compared to acetazole amide (diamox), an already established diuretic which also acts by inhibition of carbonic anhydrase.

(2) Cardrase is equally as potent as diamox in its ability to increase water and sodium excretion.

(3) The diuretic-toxic range of cardrase is more narrow than it is following the administration of diamox. Therefore, the smallest dose which will produce maximum diuresis should always be used. It appears that 250 mg per day is the maximal dose which should be used. A dose of 125 mg per day produces nearly maximum diuresis. When doses of 125 mg are used, side effects are minimal and are no more severe than those observed with the administration of diamox.

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Reports on Therapy

A Study of the Effectiveness of Mercurial Diuretics in Treatment of Cardiac Decompensation*

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Omaha, Nebraska

A NUMBER of mercurial diuretics are available to the physician interested in the treatment of heart disease. The effectiveness of individual diuretics in producing rapid and sustained diuresis, loss of weight, and return to compensation has been extensively detailed in numerous publications.[1–4] A consideration of this work led to the conclusion that a comparative study of the relative effectiveness of four mercurial diuretics which are now available and in common use would be informative.

Two previous studies[5,6] have been reported on diuretics in general use in the 1940–50 decade when mercuzanthin, Mercuhydrin®, salyrgan theophylline and Thiomerin® were studied. It was reported then that each of these were effective in producing 3 lb weight loss daily after injection. Other studies[7,8] later have indicated that the route of administration is the major factor in determining the rapidity and extent of response in weight loss from a given dose of the mercurial.

Careful consideration of several studies[9,10] which postulated that the mercurial diuretics of different composition might exert their action on different portions of the distal and proximal tubules also suggested that a study of their comparative effectiveness in producing weight loss, return to compensation and maintenance of electrolyte balance might indicate a preference for one diuretic over the others by the practicing clinician.

Method

Sixty-two decompensated cardiac patients were admitted to the study in a random fashion based on hospital registry numbers. The usual criteria for the presence of congestive failure were used, supplemented by venous pressure and circulation time. Appropriate cardiac treatment was administered including digitalis (digitoxin or digitalis leaf), bed rest, 200 mg and 600 mg sodium diets as indicated, water *ad lib.* (hospital water supply containing 140 mg sodium/liter) and ammonium chloride gram 1.0 four times daily. Mercurial diuretics were administered as follows: 0.5 ml was administered intramuscularly or subcutaneously as a test dose after appropriate electrolyte studies were obtained. If no untoward effect occurred 1 ml was given by the same route at bedtime of the same day and 1 ml the following morning on arising. If a smooth diuresis was not forthcoming by this amount of mercurial, additional increments of 1 to 2 ml were given daily or every two or three days as needed.

On admission serum sodium, potassium, chloride, CO_2, BUN, and total proteins were obtained. Daily weights were recorded for each patient along with intake and output. Each patient was followed in this study until he reached a dry weight. On completion of diuresis the serum electrolytes were restudied in the same fashion as on admission. The diuretics which were used were meralluride (mercuhy-

* From the Medical Service and Medical Research Laboratory, Veterans Administration Hospital, Omaha.

drin), mercaptomerin (thiomerin), mercumatilin (Cumertilin®), and merethoxylline (Dicurin®). These were organomercurials in which the mercury radical was attached to an organic base. The amount of mercury which was given with each cc of injection varied slightly from one organomercurial to the next but ranged from 38 mg/ml to 40 mg/ml.

TABLE I

Estimates of Serum Protein and Renal Function

Number of patients	Diuretic	Mean total serum protein g/100 ml	Mean 15 min PSP excretion, %	Mean BUN mg/100 ml
27	Mercuhydrin	6.3	19.1	18.5
14	Thiomerin	5.9	12.0	24.6
13	Cumertilin	5.8	21.3	21.9
13	Dicurin	6.4	26.2	23.1
67	Total group	6.00	18.9	21.30

Results

The data obtained have been organized in the following tables for ease of presentation. Table I presents the total serum protein and renal function in four groups studied. Table I demonstrates that the mean total serum protein is not significantly different for each of the four groups. The 15-min PSP excretion was somewhat depressed from the average norm of 25 per cent excretion in 15 min, with the maximum depression occurring in the thiomerin group.

TABLE II

Weight Loss per Diuretic and Days to Dry Weight

Diuretic	Weight loss, lb				Days to dry weight			
	Minimum	Maximum	Mean*	Standard deviation	Minimum	Maximum	Mean*	Standard deviation
Mercuhydrin	3.25	52.50	15.06	10.75	2.00	30.00	11.23	7.33
Thiomerin	4.00	31.00	13.50†	7.43	1.00	17.00	10.58	4.90
Cumertilin	4.00	34.00	17.87	10.24	5.00	13.00	8.92	2.28
Dicurin	4.00	23.50	22.27†	7.15	6.00	16.00	11.28	3.15

* Fisher's F test reveals these differences of the mean are not significant at the 0.05 level of probability.

† These mean differences are not significant on the "t" test at the 0.05 level of probability (Table 3.8 and Table 10.7—Snedecor: *Statistical Methods*, 1946).

TABLE III

Initial Mean Sodium and Potassium Levels

Diuretic	Sodium			Potassium		
	meq/*l*	Standard deviation	"t"*	meq/*l*	Standard deviation	"t"†
Mercuhydrin	137.10	6.25	0.996	4.73	0.493	0.62
Thiomerin	139.20	5.66	0.377	4.73	0.760	0.79
Cumertilin	141.33	4.83	0.152	4.72	0.365	0.34
Dicurin procaine	138.57	6.85	0.371	4.48	0.570	0.09
Total congestive failure	139.58	7.50	0.85	4.74	0.557	0.12

Mean and standard deviation: (220 hospital patients) = potassium 142.34, 8.34; sodium 4.56, 0.27.

* These differences are not significant at the 0.05 level of probability.

† These differences are not significant at the 0.05 level of probability (Table 3.8—Snedecor: *Statistical Methods*, 1946).

There also occurred a depression of the mean TSP to 5.9 and elevation of the BUN to 24.6 suggesting a somewhat greater degree of renal insufficiency in this group prior to mercurial diuresis. The mean BUN was slightly elevated at the upper limits of normal for all groups except the mercuhydrin group. These findings are consistent with the known effects of congestive failure on kidney function.

Weight loss per diuretic and days to dry weight were determined and are presented in Table II. As may be seen, weight loss per diuretic dose was at a satisfactory level for all four mercurials. Cumertilin and dicurin produced a somewhat greater total mean weight loss. All four diuretics performed satisfactorily in returning patients to dry weight in eight to eleven days on the average. Cumertilin appeared to be the most rapid in this action, mercuhydrin and dicurin taking the longest period of time to return the patients to dry weight. The differences, however, were not significant as measured by the F test.

The initial mean sodium and potassium serum levels were obtained in each of the groups and these were compared with the mean for 220 patients hospitalized in our hospital who were not in congestive failure and had no electrolyte imbalance (Table III). It was noted that the initial mean sodium levels for mercuhydrin, thiomerin, cumertilin and dicurin were not essentially different in themselves and showed no significant difference when tested by the "t" test from the hospital norm. Potassium levels also were not essentially different in each group nor were they significantly different from the mean potassium level for 200 hospitalized patients.

Table IV presents the final mean sodium and potassium levels after treatment with mercurial diuretics and of the groups studied only that using mercuhydrin was significantly different (with the "t" value of 2.10) from the pre-treatment mean. None of potassium serum levels was significantly different in any of the diuretic groups from that of the mean of the hospitalized patients. Of the groups studied three patients treated with mercuhydrin fell below 130 meq/*l* of sodium and two patients on mercuhydrin fell above 150 meq/*l* after reaching dry weight. The mean potassium serum levels were in excess of 5.5 meq/*l* three times in the mercuhydrin group, four times in the thiomerin group and twice in the cumertilin group. In general it can be said from these data that the mean sodium serum levels after treatment reveal a slight but statistically significant lowering by 2.9 meq/*l* of sodium chloride per liter from the pre-treatment mean in the mercuhydrin group only and was to be expected by the known pharmacologic action of the diuretic. This

TABLE IV

Final Mean Sodium and Potassium Levels after Treatment with Mercurial Diuretics

Diuretics	Sodium				Potassium			
	Below 130 meq/*l*	Above 150 meq/*l*	Mean serum level meq/*l*	"t" of mean difference*	Below 3.1 meq/*l*	Above 5.5 meq/*l*	Mean serum level meq/*l*	"t" of mean difference*
Mercuhydrin	3	2	133.91	2.10†	0	3	4.75	0.08
Thiomerin	0	0	134.20	1.87‡	0	4	5.07	1.09‡
Cumertilin	0	0	141.58	0.04	0	2	4.68	0.10
Dicurin procaine	0	1	138.40	0.04	0	1	4.76	0.06
Total group	3	3	136.62	0.14	0	10	4.80	0.003

Mean and standard deviation (220 hospital patients) potassium = 142.34, 8.34; sodium = 4.56, 0.28.

* "t" of mean difference = "t" of difference of means before and after diuretic.

† Significant at 0.05 level of probability.

‡ Not statistically significant at the 0.05 level of probability (Table 3.8—Snedecor: *Statistical Methods*, 1946).

decrease, however, did not exceed the lower normal limit of serum sodium in more than three cases, and all of these occurred with mercuhydrin. In three cases on mercuhydrin the final serum sodium value exceeded 150 meq/*l*. Mean serum potassium levels after treatment did not differ significantly with those before treatment or with levels of other hospital population. Ten cases were noted, however, where the serum potassium exceeded 5.5 meq/*l* which is the normal upper limit in our laboratory. These excesses were divided between the three diuretics: mercuhydrin, thiomerin and cumertilin.

Table V, comparison of initial and final chlorides after treatment with mercurial diuretics, revealed no significant difference between the initial and final chloride mean levels when tested against the hospital laboratory norm and against each other. A further comparison was made of initial and final carbon dioxide (Table VI) concentration before and after treatment with mercurial diuretics and it was noted again that there were no significant differences between the two levels, that they all fell with one exception (that of the mean final CO_2 level for cumertilin) between the hospital norm of 23-30 mm/*l*.

Discussion

The results presented heretofore demonstrate essentially no clinical or statistical differences among the four mercurial diuretics studied, with reference to weight loss, days to dry weight, or development of electrolyte imbalance. We believe that the relative effectiveness and safety of each of the diuretics used in this study stems from the adjunctive medical and dietary regimen.

TABLE V

Comparison of Initial and Final Chlorides after Treatment with Mercurial Diuretics

Diuretic	Before			After			
	Below 94 meq/*l*	Above 102 meq/*l*	Mean	Below 94 meq/*l*	Above 102 meq/*l*	Mean	"t" of mean difference*
Mercuhydrin	3	16	97.62	3	7	100.04	0.74
Thiomerin	4	6	97.00	3	3	97.32	0.07
Cumertilin	7	6	94.21	5	4	92.70	0.20
Dicurin	5	2	86.17	4	2	89.82	0.18

Hospital laboratory norms—Cl 94 to 102 meq/*l*.

* These differences are not significant at the 0.05 level of probability (Table 3.8—Snedecor: *Statistical Methods*, 1946).

TABLE VI

Comparison of Initial and Final CO_2 Combining Power after Treatment with Mercurial Diuretics

Diuretic	Below 23 mm/*l*	Above 30 mm/*l*	Mean CO_2 before	Below 23 mm/*l*	Above 30 mm/*l*	Mean CO_2 after	"t" of mean difference
Mercuhyrin	6	3	24.68	7	3	23.96	0.37
Thiomerin	8	1	23.00	4	1	23.70	0.28
Cumertilin	7	0	25.54	3	0	21.56	1.66*
Dicurin	2	2	27.66	0	3	34.68	1.49*

Hospital laboratory norms—CO_2 23 to 30 mm/*l*.

* Mean differences are not significant at the 0.05 level of probability (Table 3.8—Snedecor: *Statistical Methods*, 1946).

Previous studies[2-4, 6, 17] have shown only slight differences between the effectiveness of some mercurial diuretics in producing diuresis and weight loss through edema mobilization. The differences reported have been due largely to the route of the drug used. Our study is in agreement with this and in addition shows that no significant electrolyte disturbances occur in the majority of patients in which the regimen we have described is followed.

Although this study did not demonstrate that electrolyte disturbances follow diuretic therapy in the greater majority of patients, conditions such as hyponatremia, hyperchloremia and hypokalemia do occasionally occur and are noted. In addition, rare sensitivity reactions do occur and mercurialism may present in patients especially sensitive to mercury. In this group there were two cases of hypersensitivity to mercury (dermatitis medicamentosa with exfoliation secondary to mercaptomerin), which required stopping of the mercurial diuretic and substituting a non-mercurial diuretic. Both patients responded promptly to treatment by withdrawing the offending mercurial. Two cases of hyponatremia were observed which were in patients with far-advanced heart disease and cor bovinum who required multiple daily injections of mercurial diuretic of the order of 80 mg/day. The hyponatremia was thought to be a function of their far-advanced myocardial degeneration which did not respond to any therapy. Other observers[16] report that the persistence of hyponatremic state is an ominous sign, commonly produced by cardiac or renal failure, with a mortality of approximately 50 per cent.

A number of years ago it was demonstrated that maximum diuresis occurred with 1.5 ml of the mercurial diuretics then available and larger doses did not yield a significantly and therapeutically greater increment.[11] The well-known toxicity resulting from the chronic use of larger doses of mercurials with the retention of mercury leading to mercurialism or hyponatremia has led us to limit mercurial injections in amount and frequency to that actually required for the smooth elimination of edema fluid.[12,13] These amounts optimally are in the region of 1 ml of diuretic solution containing 38 to 40 mg of organic mercury intramuscularly or subcutaneously on the average, although an occasional patient required 2 ml containing 76 to 80 mg of organic mercury.

Since sodium plays the greatest role in edema formation, this ion was interdicted in our investigative situation through the medium of low sodium 200 to 600 mg diets. The action of the mercurial diuretic may be potentiated by maintaining adequate serum chloride levels. It has been shown during diuresis that chloride is lost at a greater rate than sodium.[14,15] Hence for this reason ammonium chloride is administered in 3 to 4 g daily doses. In rare cases where diuresis does not follow this regimen, it may be necessary to give ammonium chloride in 6 to 8 g daily doses for three or four days to summate the diuretic effect of acid salts with that of the mercurial diuretic. Water and beverages may be given *ad lib* according to thirst except where saline content is high, or where refractoriness to diuretics is encountered. Recent studies of the low-salt syndrome incriminate overhydration as the etiology of hyponatremia and show that this condition can be treated successfully with acetazolamide, ammonium chloride and mercurial diuretics.[16]

Summary

This study has been conducted on 62 decompensated cardiacs who were subjected to diuresis with four mercurial diuretics. Studies on weight loss and days required to return to dry weight revealed a small difference between meralluride, mercaptomerin, mercumatilin and merethoxylline, which was not significant, indicating that these drugs may be used interchangeably. The serum electrolytes of these patients revealed no significant difference from those of other hospital patients. Following diuresis with mercurials to dry weight, no clinically significant differences were noted in the sodium serum levels, except in the case of mercuhydrin where there was a statistically significant decrease in the serum sodium level. This was not within the pathologic range nor did it result in hyponatremia except in two cases noted in patients with far-advanced congestive failure, cor bovinum and myocardial degeneration. Two cases of medicamentosa dermatitis with thiomerin were also found which responded

promptly to withdrawal of the mercurial and substitution of a non-mercurial diuretic. It is felt that the low sodium syndrome cannot be related to any one mercurial diuretic but rather to the method in which the diuretic is used in the treatment of congestive failure.

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The Effectiveness of Rolicton®, a New Oral Diuretic, in Severe Cardiac Failure*

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SEVERAL diuretics are available for use in cardiac failure: the mercurials, the carbonic anhydrase inhibitors, the aminouracils, the acidifying salts such as ammonium chloride, and the xanthines. These five groups are all relatively safe and effective.

This study concerned the use of a new oral diuretic, Rolicton®† (aminoisometradine), in patients with edema, whatever the cause.

METHODS AND MATERIALS

Two groups of patients were studied. One group consisted of ten gravely ill patients, with severe symptoms and extreme cardiac failure; the second group, those with mild to moderate symptoms. In the first group, patients generally refractory to treatment, the diuretic was used in conjunction with other agents. In the second group the medication was given generally as a primary therapy or with one other drug such as digitalis.

There were 89 patients in all, ten very seriously ill, and 79 with mild to moderate edema or congestive failure. Since this was a clinical study the improvements in subjective and objective signs and symptoms were used as a guide to the effectiveness of therapy. These consisted of: improvement of dyspnea, loss of edema and rales, and weight loss.

Rolicton, a brand of aminoisometradine, is 1-methallyl-3-methyl-6-aminotetrahydropyrimidinedione. It is a white, crystalline substance which is water soluble. It is available in 400 mg tablets, and is classified as an aminouracil. It is related to Mictine®, a brand of aminometramide.

The following is a classification of the causes for the edema and the number of patients in each group: congestive heart failure, eighty; renal disease, three; hepatic disease, three; other diagnoses, three. The largest group, those with cardiac failure, included 24 patients with rheumatic heart disease, 33 with hypertensive cardiovascular disease, and 33 with arteriosclerotic cardiovascular disease, including coronary heart disease. Nineteen patients were hospitalized and 70 seen as outpatients. Not included in this series were two patients who stopped taking the tablets after 12 hours of administration; one complaining of a sensation of heat, the other of nausea.

RESULTS

The results of treatment are summarized in Table I. It will be noted that this diuretic appears most effective in cardiac failure though the number of patients with renal, hepatic, and other disorders numbered only nine. The three miscellaneous conditions were dependent edema

TABLE I

Summary of Diuretic Effect

	Excellent	Good	Fair	Poor	Total
Cardiac disease	52	12	10	6	80
Hepatic disease	0	0	1	2	3
Renal disease	0	0	0	3	3
Others	0	0	2	1	3

* From the Medical Services, Cook County Hospital and the Chicago Medical School, Chicago, Illinois.

† Obtained through the courtesy of G. D. Searle Co., Chicago, Illinois.

of unknown etiology in two cases and generalized edema possibly related to excess antidiuretic hormone of the pituitary in one case.

The greatest dramatic diuretic effect was noted in ten patients, all of whom had severe cardiac failure, Class IV.[1] In this group there were four patients with rheumatic cardiovalvular disease, four with arteriosclerotic cardiovascular disease, and two with hypertensive disease.

Case Histories

Case 1. W. H. The patient, a 46-year-old white male, had rheumatic cardiovalvular disease with aortic stenosis and mitral insufficiency. For the previous ten years he had been completely incapacitated most of the time. He was either in bed at home, or at a hospital. During the previous 18 months he was unable to leave his home because of severe anasarca, dyspnea, rales in both lung bases and at times hemoptysis. He refused hospitalization and medicated himself, keeping an excellent diary of his therapy and response.

His therapy consisted of 2 cc of Thiomerin® that he administered himself subcutaneously three times a week, Crystodigin® 0.2 mg daily, low-salt diet, oxygen by mask when necessary, Diamox® 1 tablet daily, Resodec® 6 tablespoons daily, and ammonium chloride 65 grains on the day prior to an injection of thiomerin. From May, 1956 to June, 1956 his weight increased from 139 to 146 lb. He became increasingly short of breath and it was necessary to give him injections of mercuhydrin 2 cc intravenously once or twice a week to keep him partially comfortable.

On June 6, 1956 he started taking rolicton 1,800 mg a day or four and one-half tablets. No reaction to rolicton was noted. He discontinued the diamox and ammonium chloride. From June 6 to 10 his weight remained stationary, but he subjectively improved using less oxygen. Over the next seven days he lost 8 lb. During the next two weeks he lost 3 lb.

Both objectively and subjectively he was markedly improved. The thiomerin was reduced to 2 cc every ten days and he did not need oxygen. He remained on resodec, crystodigin, phenobarbital, and a low-salt diet. On his own he cut the rolicton to 800 mg a day and for two weeks he maintained the same weight. Gradually he gained 3 lb up to 138 lb and on the resumption of 1,800 mg daily his weight over the following nine-day period dropped to 134 lb. It remained at that level for one month. During September, 1956 his weight again began to increase and despite increasing doses of rolicton to 2,400 mg a day, increased frequency of injections of thiomerin and mercuhydrin, he began to develop more evidences of cardiac failure and finally in October, 1956 he expired.

Case 2. E. H. This patient, a 78-year-old colored female, had been ill with severe dependent edema for three years. Arteriosclerotic cardiovascular disease with auricular fibrillation was present. She had been treated with a low-salt diet, mercurhydrin 2 cc weekly, Carbo-resin® 6 tablespoons daily, digitoxin 0.2 mg a day, and ammonium chloride 90 grains daily for four out of every seven days. Her weight rose from 145 to 149½ lb from May 1 to May 14, 1956. She entered the hospital on June 1 because of increasing dyspnea. The ammonium chloride and carbo-resin were discontinued and rolicton was begun in a dose of 600 mg a day. The weight dropped 10 lb in the ensuing 14-day period. The only other factors could have been the rest at the hospital and more rigid dietary control. As an outpatient in the past eight months her weight has been maintained on the same regime and she is generally symptom free.

Case 3. M. S. This patient, a 69-year-old white female with arteriosclerotic cardiovascular disease, diabetes and heart failure, had been responding well to mercurials 2 cc weekly, digitoxin 0.2 mg daily, diamox 2 tablets daily, low-salt diet, and 20 units of insulin daily. Her weight on February 1, 1956 was 155 lb, but by April 27, 1956 it rose to 168½ lb. She became extremely dyspneic and had severe dependent edema.

Using the same therapy with the addition of rolicton 1,800 mg a day over the next five weeks, her weight dropped to 156 lb. About four weeks later she developed chest pain. Acute coronary insufficiency with left heart failure was diagnosed. Intravenous mercuhydrin and a more rigid restriction of salt relieved her symptoms. She is now maintained on digitoxin 0.2 mg daily, a low-salt diet, mercuhydrin once weekly, 800 mg rolicton daily, and her usual dose of insulin.

Side Effects

Ninety-one patients were given this new oral diuretic. Two patients were unable to continue the drug after the first 24 hours and were not included in a study of its diuretic efficiency. One of these two patients complained of a feeling of generalized heat without fever that did not recur when the therapy was discontinued. The other complained of nausea. Of those who continued the drug, one noticed a transient rash that may have been related to an activated rheumatic process. Five patients mentioned nausea that disappeared on continuing the therapy.

There were no apparent effects on liver function studies completed on four of the patients, or on the blood urea nitrogen completed on 34 of the patients. All of the patients had repeated blood counts and urinalyses without demonstrable change.

Conclusions

Friedberg[2] states: "It would be highly desirable to obtain a diuretic agent which could be given orally and yet act as effectively as parenterally administered mercurial diuretics, without producing toxic manifestations." Rolicton appears to be a step in the right direction. It probably inhibits the tubular reabsorption of sodium as reported with mictine, a brand of aminometradine.[3] The advantage of rolicton seems to be in the apparent lack of side effects. This allows a larger dose to be used more continuously. The use of mictine was associated with a much greater incidence of side effects.[4]

Other diuretics such as acetazolamide,[5] mercurials,[6] ammonium chloride,[7] and the xanthines[6] all appear to have side effects and demonstrate varying degrees of diuretic efficacy.

Rolicton cannot supplant the other diuretics, but it has proved very useful in this study with cardiac patients who are refractory or need maintenance therapy.

Summary

(1) Aminoisometradine (rolicton) a new oral diuretic, was administered to 91 patients.

(2) Of the 89 patients who maintained the drug, excellent or good results were obtained in 64 cases or approximately 72 per cent; 13 patients or 15 per cent had fair results; and 12 patients or 13 per cent had poor results.

(3) The drug appeared to be most effective in cardiac failure, though only nine patients with hepatic, renal or other diseases were studied.

(4) Eight of the 91 patients had some side effect. Two discontinued the drug. Six had nausea, one of whom stopped the therapy; the other five were able to continue and the nausea disappeared.

(5) It is concluded that aminoisometradine is an effective, well-tolerated oral diuretic that can be tried in refractory cases of cardiac failure in conjunction with other therapy. It appears to have its greatest usefulness for maintenance in mild to moderate degrees of cardiac failure.

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Historical Milestones

Rheumatic Carditis: Bouillaud and Some Unknown Irish Precursors

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IN FAMILIAR histories of medicine Jean-Baptiste Bouillaud (1796–1881) is traditionally regarded as the principal founder of our knowledge of rheumatic carditis. His reputation in this subject is based securely on his famous "law of coincidence" between rheumatic arthritis and carditis (1836)[1] and on the further observations published in his Clinical Treatise on Articular Rheumatism (1840).[2] Herewith are translated excerpts from the earlier work.

BOUILLAUD'S LAW OF COINCIDENCE

It is, I will venture to say, a discovery worthy of some attention, to wit, the almost constant coincidence, either of endocarditis, or of pericarditis, or endo-pericarditis, with violent acute rheumatism. This fact, which daily observations more and more confirm, is of such vast importance that it constitutes, in some measure, a true revolution in the history of acute articular rheumatism. I am not at all astonished that so many are opposed to it: that is the fate of all new truths of any importance. But what I am not afraid to predict is, that but a short time hence it will scarcely be conceived how so evident a fact could have been concealed from the scrutiny of physicians who preceded us in their observations.

In auscultating the sounds of the heart in some individuals still labouring under, or convalescing from, acute articular rheumatism, I was not a little surprised to hear a strong, file, saw, or bellows sound (*bruit de rape, de scie ou de soufflet*), such as I had often met with in chronic or organic induration of the valves, with contraction of the orifices of the heart. Now nobody would suspect an affection of this kind amongst the majority of persons who suffered from rheumatism and were submitted to our examination. Many of them were for the first time affected with articular rheumatism, and had hitherto enjoyed the most perfect health. I then called to mind other cases of acute disease of the heart, during the course of which I had heard the bellows and file sounds, and I resolved to explore, attentively, the heart and its functions in all those affected with rheumatism whom I should meet with. Thanks to this exploration, I soon discovered that an acute affection of the heart was not a simple accident, a rare, or as it were fortuitous complication, but in truth the most usual accompaniment of this disease.

The coincidence of endocarditis with acute articular rheumatism, is, to our minds, certain, when the following signs are present.

Bellows, file, or saw sound in the precordial region, with a dullness of this part on percussion, to an extent much more considerable than that in the normal state, and which, also, sometimes presents, but in a less degree than in pericarditis with effusion, an elevation or abnormal arching; the movements of the heart elevate with force the precordial region; and they are often irregular, unequal, intermittent, and accompanied at times with a vibratory trembling. The pulse is hard, strong, vibrating, unequal and intermittent, like the beatings of the heart.

It appears from the above that there are signs common to pericarditis and endocarditis, and that the differential physical signs are not always well marked. Cases, also, present themselves in

which it is difficult enough to determine whether there is pericarditis or endocarditis, and whether one of these affections, once well recognized, exists alone or combined with the other. These are the cases in which pericarditis may be present without an evident effusion, and with a production only of false membranes. Then, indeed, the beatings of the heart are sensible to the touch, as in simple endocarditis, and the saw and bellows sound, the vibratory trembling of the precordial region, may be present in this case as in endocarditis.

From the beginning of August, 1835, to that of October following, I have met with twenty new cases of articular rheumatism, either recent or of some standing, of which the following is the description under the point of view which now engages our attention.

I have placed these twenty cases under three heads. The first comprises those relating to general acute articular rheumatism, accompanied by fever of more or less violence.

The third head is confined to cases of mild articular rheumatism, without fever.

Between these two I have placed a second division, containing cases in which a lesion of the heart, called organic is met with in individuals formerly affected with prolonged acute articular rheumatism, and in which relapses had occurred. This head is closely allied to the two others; it supports the first, and reciprocally, is supported by it. In fact, only half of a disease is known when it is studied in the acute stage alone. To know it fully it must also be examined in the chronic stage. Now what is this organic lesion of the heart in subjects formerly affected with articular rheumatism, if not endocarditis and pericarditis in a chronic form? that is to say, with accidental productions, transformations, thickening and induration of tissues formerly inflamed, etc.

Let us begin with the four last cases (17–20) in which the rheumatism was without fever. In respect to them we would only remark, that they existed without any affection of the sero-fibrous tissues of the heart. They confirm what we have already said of similar cases before observed, viz., that the law of coincidence of endocarditis and pericarditis with an acute articular rheumatism, does really apply, with some few exceptions, only to cases in which this disease is diffused and accompanied by fever.

Among the nine cases of the first head, six exhibited the most certain signs of rheumatic inflammation of the serofibrous tissues of the heart (1–3, 7–9). In the three other cases this coincidence was less evident; nevertheless it existed really in two of them (4, 5) and in one only it appeared to be doubtful (6).

Thus then in eight times out of nine, an acute rheumatism of many joints was accompanied by rheumatism of the sero-fibrous tissues of the heart. The seven cases comprised under the second head cannot be taken into regular account in the present question, since the organic affection of the heart (to which was joined in some patients an organic lesion of the aorta) was not connected with articular rheumatism actually existing, but rather with old attacks of that malady. Could it be indeed by chance that out of seven cases of this disease not one would be found in which it was not preceded by a violent rheumatism of long continuance? Could such an opinion be sustained in opposition to those other facts which show that an acute articular rheumatism, actually existing, is so often accompanied by endocarditis or pericarditis, that is to say, of rheumatism of the sero-fibrous tissue of the heart? Would it not be more correct to admit, as we have elsewhere endeavoured to demonstrate, that it is to this last affection, illy understood till now, that we must attribute a large portion of the lesions of the heart called organic.

In fine, can we from these new cases be accused of exaggeration in saying, that in one-half of the instances of diffused acute articular rheumatism with much fever, the sero-fibrous tissue of the heart is found affected in like manner as the joints?

Ought we not on the contrary to make a formula of the law of coincidence, as follows: In the great majority of cases of diffused acute articular rheumatism with fever, there exists in a variable degree a rheumatism of the sero-fibrous tissues of the heart. This coincidence then is the rule, and the non-coincidence the exception.

Bouillaud's Precursors

It is well recognized that Bouillaud, like many if not all discoverers, had his precursors, includ-

ing Wells of Charleston, Pitcairn, Baillie, Jenner, and others. In addition to these celebrated men there were some anonymous precursors, not mentioned in the textbooks and anthologies. The evidence is found in Benjamin Rush's famous book *An Account of the Bilious Remitting Yellow Fever*. . . Philadelphia, 1794, pp. 43–44. In a discussion of the pulse in yellow fever, Rush says:

"In a letter I lately received from Mr. Hugh Ferguson, a student of medicine in the college of Edinburgh, written from Dublin, during the time of a visit to his father, and dated September 30th, 1793, I find a fact which throws additional light upon this subject. 'A case' (says my young correspondent) 'where a remarkable intermission of pulse was observed, occurred in this city last year. A gentleman of the medical profession, middle aged, of a delicate habit of body, and who had formerly suffered phthisical attacks, was attacked with the acute rheumatism. Some days after he was taken ill, he complained of uncommon fullness, and a very peculiar kind of sensation about the praecordia, which it was judged proper to relieve by copious blood-letting. This being done, the uneasiness went off. It returned however three or four times, and was as often relieved by bleeding. During each of his fits (if I may call them so), the patient experienced an almost total remission of his pains in his limbs; but they returned with equal or greater violence after the blood-letting. During the fit there was an intermission of the pulse (the first time) of no less than thirteen strokes. It was when beating full, strong, and slow. The third intermission was of nine strokes. The gentleman soon recovered, and has enjoyed good health for ten months past. *The opinion of some of his physicians was, that the heart was affected as a muscle, by the rheumatism*, and alternated with the limbs.' " (Italics not in original.)

Ferguson's letter to Rush proves that the clinical diagnosis of rheumatic disease of the myocardium was being made in Dublin as early as 1792. Whether the diagnosis was correct in the case cited, each cardiologist reader may decide for himself.

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"True Rheumatism"—V. T. Talalayev

The Viewpoint of a Russian Pathologist

ARNOLD LIEBERMAN, M.D.

New York, New York

THIS SLIM 200-page volume of the "Collected Works" of V. T. Talalayev was issued by the State Publishing Press in Moscow in 1953. It is in the nature of a memorial volume to Professor Talalayev who had died in 1947. His successor in the Chair of Pathology at the University of Moscow, Professor Abrikosov, explains in the foreword that the committee had decided to select only the work Professor Talalayev had done on Rheumatic Fever. Abrikosov states that rheumatism had been Talalayev's primary interest and that Talalayev's work on rheumatism is "the greatest contribution Soviet science has given to world medicine."

Also, in the foreword there is the statement that in 1936 Dr. Talalayev was awarded first prize by the International Rheumatic League for his monograph "True Rheumatism" and that this volume forms the basis for the present book being discussed. The committee has taken the most pertinent extracts from that monograph plus extracts from some 70 of his published works which are listed in the back. In bringing the material up to 1953, the editorial committee has merely added clarifying notes and comments, clearly so labeled. Essentially, then, this volume is a summary of the work done by Talalayev between World War I (and before) up to about 20 years ago. In the list of titles, no publications bearing directly on rheumatism are dated later than the thirties. Possibly some of his papers on "Allergy," etc., touch on it but all references are to unavailable Russian journals.

The outside of the book is quite unprepossessing and so one is all the more pleased with the contents. Considering the fact that the bulk of this work seems to date back 30 and even 40 years, the style of the approach is most modern, crisp, and clear. The author plunges unhesitatingly into a most illuminating discussion of many of the controversies still besetting the topic.

HISTORICAL ASPECTS

The introductory chapter outlines the author's reasons for devoting practically his entire scientific life to research in the field of "true" rheumatism. He traces the history of the subject, quoting Prosper Alpinus, Sydenham, Cullen and others. Then he gives it the name "Bouillaud's Disease" for the reason that it was this clinician who first clearly associated "true" rheumatism with later cardiac illness, thus, of course, differentiating it from the other arthridites. Talalayev calls attention to the numerous rheumatoid symptoms occurring during sepses of various types, giving as examples gonorrhea, scarlet fever, pneumonia, etc. These are to be carefully differentiated nosologically from true rheumatism. This Talalayev carefully defines as a specific affliction of the cardiovascular system in the course of which there develops a characteristic endomyocarditis which is the cardinal anatomic and clinical fact. The polyarthritis, when present, is only an incidental finding.

Talalayev then proceeds to explain that he will discuss his pathologic material under the three distinct clinical types of the disease: polyarthritic, cardiac and ambulatory. Nodose rheumatism and chorea minor he proposes to evaluate separately in order to avoid confusion. Each of the three basic types is further subdivided by him according to the paths taken

by the patients to the autopsy table: those dying in the first attack, in later recurrences, from other causes, and those succumbing from cardiac decompensation. Finally, he proposes to devote several chapters to a unifying clinical and theoretic discussion.

The second chapter explores quite thoroughly the history of the subject. The editorial committee inserts a note apologizing for lack of Russian references and refers to a monograph which corrects that "defect." Be that as it may, Talalayev gives Aschoff full credit for the priority in describing the specific rheumatic nodule. Then he takes up Geipel's work and takes up in minute detail the differences from periarteritis nodosa. Talalayev shows complete familiarity with the viewpoints of numerous workers, making pithy, cogent comments as he moves along. Thus, he quotes approvingly Thorel's work where this author disagrees with Aschoff and insists on an infectious (coccal) causation—and this back in 1910! Similarly, he agrees with Frank (writing in 1912) who goes into the fibrinoid nature of the very earliest rheumatic exudate.

PATHOLOGIC ASPECTS

Talalayev then plunges into the details of his own contributions to the literature of rheumatism. Numerous autopsy reports are presented in crisp, yet only essential detail. Without false modesty but with complete authority he confirms the specificity of the Aschoff bodies and elucidates his views on their nature. He notes that these may form with great rapidity. The *rheumatic nodules* may develop within hours even in an afebrile phase of the disease and may not even be very tender. He studied personally seven cases of rheumatic nodules. According to Talalayev, the entire literature, up to that point, contained only five cases. He presents in minute detail the precise staining technic used, the myxomatous edema, fibrin exudate, fibrinoid transformation of the collagenous substance and the basophilic granulation. He illustrates with microphotos the point that cellular changes are a later phenomenon. The nodes formed in fatty subcutaneous tissues resemble oleo-granulomas which are known to be inflammatory in nature. Talalayev is careful to state that Fahr, Pappenheimer, Alwin and others were conducting independent studies along similar lines.

In chapter 3, Talalayev presents his clinical material as it came to autopsy. He was able to find acute, specific lesions in 72 cases diagnosed as rheumatism. Then he presents a second group of 60 cases where typical rheumatic scleroses were found. In the anamneses of this second group, arthritic symptoms had been noted only in some 50 per cent of the total. These patients had died as a result of cardiac decompensation, septic endocarditis lenta or of incidental causes. A third group of patients proved to have fresh or chronic valvular and endocardial damage; yet the specific rheumatic lesion could not be demonstrated. These 34 cases died of sepsis, uremia with pericarditis, etc.

There follows a discussion of Tandler's concept of the chondroitin tissue skeleton of the heart and its relevancy to the structure of the arteries and the valves. Talalayev briefly details his exact technic in preparing the tissues for further studies. He follows with an analysis of the procedures used by others. A brief but most modern and still informative outline of the properties of the mesenchymal ground substance chondroitin, collagen and fibrils follows.

Forms of Disease: Talalayev illustrates his divisions of the disease by a diagram attached to a later chapter on page 169. These are shown in the schemata in Figures 3 and 4. The main forms of the illness he gives as: (a) polyarthritis rheumatica—eight cases; (b) cardiac form without joint symptoms—three cases presented in meticulous detail; (c) ambulatory or "mute" rheumatic fever without joint or serous surface involvement, i.e., a pure carditis and vasculitis—five cases presented in great detail.

The final portion of chapter 3 (which is far and away the longest in the book) is devoted to *complications* of rheumatic fever: (a) nodose type—seven cases; (b) chorea minor—five cases, with careful studies of such tissues as serial sections of the strial bodies, the pons, medulla oblongata, substantia nigra, cerebellum, sympathetic ganglia, etc.

A final group illustrates Talalayev's views

as to the length of time a "pure" rheumatic lesion takes to run its course. Every one reading this review should take an earnest look at the schema in Figure 1. The reader today

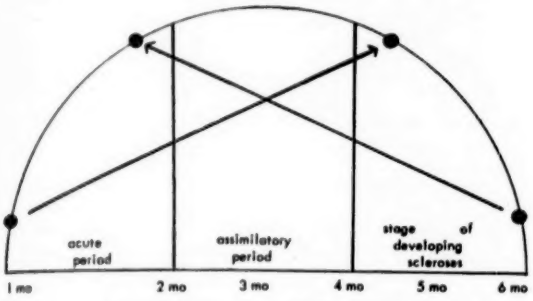


Fig. 1. Adapted from p. 96 of *True Rheumatism*

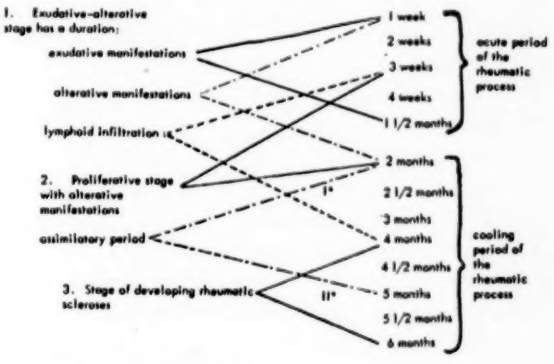
can well take to heart Professor Talalayev's earnest plea to the clinician never to forget that the *minimum healing time* is six months, never less and frequently more.

This chapter is really the core of the book and well worth reading again and again by any one interested in rheumatism. It is a model of clear, compact reasoning and a brilliant presentation of a tremendous mass of clinical material coming to the autopsy room. The great care with which Talalayev marshals his data in support of the schema in Figure 1 (the reasons for assigning six months to the evolution of a rheumatic lesion) is in the very finest scientific tradition. Again, the data on chorea is enormously impressive, as good as anything that this writer has found available.

The histogenesis of the rheumatic process is the theme of chapter 4. The schemata in Figures 1 and 2 are only a feeble reflection of Talalayev's pedagogic clarity. He presents microphotographs of the precellular phase of the lesion: the exudative-alterative stage. He details the myxomatous edema with the marked basophilia brought out by his technics. He shows photos with collagen fiber changes; the ground substance changes as the albumins precipitate; the transition differentiating exudative from degenerative; and, finally, the ending of the acellular phase as lymphoidal infiltration develops. The initial connective tissue hypertrophy develops quickly, these cells becoming gigantic.

The well-known *Aschoff body* is detailed through the phases of proliferation and assimilation. The rheumatic scleroses are then brought into their places in the diagrams already mentioned. Microphoto after microphoto brings out how the granuloma evolves, how the giant cells orient themselves on the albumin masses, exactly what does occur during necrobiotic alterations—the entire complex picture with a wealth of illustrative comment and analysis. Rather interesting is the parallel drawn to the known reaction to cat-gut sutures. The final paragraph summarizes again the essence of his views and is a model of lucid simplicity.

After giving in a couple scanty chapters the "banal" thromboses, and other changes accompanying the specific lesions, Talalayev returns in chapter 7 to his reasons for saying, " 'rheumatic myocarditis' is the decisive criterion for the histologic diagnosis of the disease." He presents his reasons for believing joint changes to be equivocal. Then, he accepts the word "rheumatism" as having clinical



*I Individual nodes can appear in 2nd week and even by end of 1st week.

*II Rheumatic nodes which appeared in first weeks of illness can end their fibrotic metamorphosis even earlier.

Fig. 2. Adapted from p. 157 of *True Rheumatism*

sanction even if the root word "rheuma" can no longer be accepted in its original sense. He agrees that chorea minor is absolutely rheumatic in nature even if an occasional case (as his patient with chorea gravidarum) fails to demonstrate the specific lesion.

In chapter 7 the detailed analysis of the *histology of the "rheumatic triad"* is expanded further. The discussion on "endocarditis valvularis et chorditis (tendinae) myxomatosa rheumatica diffusa" is as good today as when

written in the twenties. The details of the precise localization of the lesions and the particular vulnerability of the bundle of His

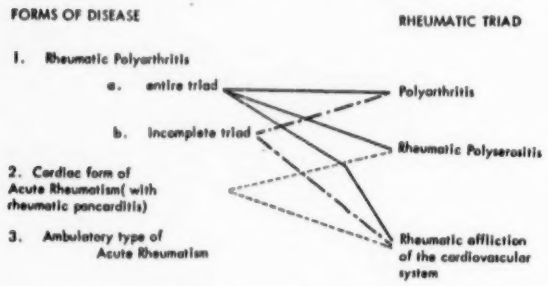


Fig. 3. Adapted from p. 169 of *True Rheumatism*

is truly excellent. Talalayev presents Coombs' cases, parallels them with his own and then states his accord with Coombs' views on the specific nature of the rheumatic serositis lesions. Rheumatic polyarthritis is stated as being present in only half of the patients having rheumatic fever. Talalayev presents some cogent reasons why precisely the sickest cardiacs might fail to manifest joint or tendon changes. The editorial board states, in a footnote, that this Talalayev speculation has been disproven. Present-day American thinking seems to be in accord with this footnote.

The distinction between the intra- and periarticular changes is brought out with precision. Talalayev stresses the ominous prognostic significance of the rheumatic nodules appearing under the skin, in tendon insertions, etc. Along with his own substantiating cases, he presents work done by Jurgens, Scheele, Chiari, Barlow and others. The chapter is concluded by a brief mention of erythema nodosum and of rheumatic purpura. The first is either tuberculous or rheumatic while the latter is merely a manifestation of a hemorrhagic diathesis.

In the next several chapters, Talalayev presents some further details, particularly in relation to the sympathetic and central nervous systems, as well as a speculation on the possible relationship of the rheumatic process to thyroiditis. In 1957 an article was published in the *Journal of the American Medical Association* on this disease as a manifestation of allergic response, thus giving it quite a current interest.

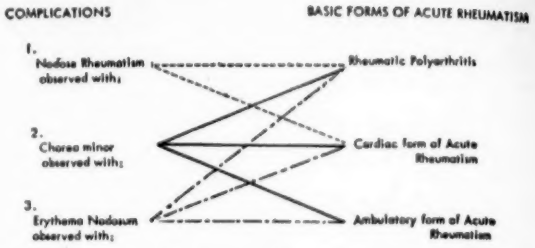

COMPLICATIONS
BASIC FORMS OF ACUTE RHEUMATISM
1. Nodose Rheumatism observed with:
2. Chorea minor observed with:
3. Erythema Nodosum observed with:
Rheumatic Polyarthritis
Cardiac form of Acute Rheumatism
Ambulatory form of Acute Rheumatism

Fig. 4. Adapted from p. 169 of *True Rheumatism*

CLINICAL ASPECTS

After having presented this succinct summary of incidental changes in other organs, Talalayev deliberately leaves the pathology amphitheater and proceeds to spell out the significance of his findings on the clinical level. The four schemata appended to this article are used to correlate much that may not be completely clear. The language is painstakingly practical on a didactic level. In chapter 13 the immensely serious question is asked, "When can the rheumatic patient be considered well, clinically speaking?" In essence, Talalayev again and again elaborates on the minimum six months as being the time taken by even a single lesion to heal. Talalayev deplores the tendency of the clinician to use the painful arthritic lesions as a sort of gauge mirroring the invisible internal lesions. He reminds the reader that patients might be discharged as "clinically well" precisely at a time when the mute cardiac lesions are creating their most terrible havoc.

There is a contemporary note in the flat assertion made by Talalayev that a minimum of two months' bed rest is essential in the lightest and shortest acute cases. Four months of further close observation are bed-rock minimum. With all the present-day debate as to the precise care of the rheumatic patient, this emphatic advice given by Talalayev so many years ago still has validity. He pithily reminds the clinician that the sole criterion of "lightness" and "severity" is the ultimate damage done to the valvular apparatus of the heart. Clinical standards being so fallible, utmost conservatism should guide the attending physician.

Chapter 14 is a recapitulation of the entire clinical discussion and is as applicable today as the year it was written. In chapter 15 there is a critical review of the still unsettled question

of the *etiology of rheumatic fever*. The streptococcic original infection and its secondary allergic repercussions and the relationship of the macro-organism to the micro-organism are presented in a manner absolutely contemporary. It is a great pity that the editors of Talalayev's work have not seen fit to incorporate some extracts from some of his later titles. The article "Allergy and Its Relation to Endocarditis" is quite intriguing. Certainly Talalayev quotes the ideas of Peyer, Pemberton, Pirquet and other pioneers in the field of allergy approvingly. When Maclyn McCarty closes his article in the December 1956 issue of *Circulation* with a plea for a further study of the streptococcus and its specific role, he is not far in advance of Talalayev pleading for the same thing twenty years ago. Also, Talalayev's approach to the meteorologic factors altering the host response is superb in its balance of discriminating judgment.

Chapter 16 is devoted to *endocarditis lenta*. Talalayev gives his reasons for the belief that this disease represents a mutational form of the original illness. Mere valve deformities alone do not form grounds for saying that we are dealing with just a focus of lowered resistance: syphilitic lesions fail to have sepsis engrafted on them.

Reporting in the *Journal of the American Medical Association* of December 14, 1935, following a summer sojourn in Russia, this writer commented on the rather low medical standards of practice then prevalent in that country. Dr. Irving Wright in reporting on "Medical Mission to Moscow" made in September 1957 felt constrained to remark that the Russians were still some five or more years behind us in their approach to medicine. "True Rheumatism" by V. T. Talalayev is the exception to prove the rule.

Altogether, this monograph has the timelessness of a true classic. It would be worth translating in toto as it makes excellent reading today. Whether it is "the greatest contribution Soviet science has given to World medicine" remains to be determined after competent authorities have made adequate comparisons with other Russian achievements. It unequivocally bears comparison with such classic monographs as those by Sir Thomas Lewis, Taussig, and other Western investigators of top stature. Professor Talalayev's monograph is well-written, concise and very informative. It is regrettable that most American workers are unaware of the existence of this work. It is hoped that the present review will fill a scientific gap.

Diagnostic Shelf

Rheumatic Heart Disease vs. Chronic Myocarditis

THE PATIENT,* a 32-year-old colored female, entered the hospital complaining of fullness in the epigastrium, exertional dyspnea, ankle edema, palpitations, anorexia, nausea, and vomiting. The patient had suffered from a sore throat accompanied by fever and a migratory polyarthritis at the age of 10, and had been hospitalized for 3 months. Apparently she was asymptomatic until the age of 27, when she developed acute heart failure. Since then the patient had suffered from numerous episodes of congestive failure requiring hospitalization. Three years prior to the last admission ascites was noticed.

PHYSICAL EXAMINATION

The patient was in acute respiratory distress and in orthopneic position; she appeared chronically ill and looked older than her age. Chest was clear on percussion; numerous crepitant rales were heard over both pulmonary bases. The heart was markedly enlarged to the left and right on percussion. Auscultation revealed a grade 2 systolic murmur and a proto-diastolic gallop at the apex. P_2 was greater than A_2. Pulse 100/min and regular; blood pressure 115/90. The abdomen was distended. The liver was palpable 3 fingers' breadth below the costal margin, and was moderately tender. There was no ascites. There was 2+ ankle edema.

In subsequent examinations, a diastolic rumble at the apex and a split P_2 were heard.

CLINICAL DIAGNOSIS

The clinical diagnosis was: rheumatic heart disease, mitral stenosis and insufficiency.

* Patient from the Cardiac Clinic of Mount Sinai Hospital, Chicago. Service patient (Dr. E. B. Freilich).

LABORATORY FINDINGS

Urine: High specific gravity, 4+ albumin, rare granular casts.

Blood: Normal Hb, RBC, WBC and differential; negative serology for syphilis; sedimentation rate was 24, 23, 46; C-reactive protein was 3+, 2+, 4+; ASO titer was 50, 12, 12; cultures were negative.

Electrocardiogram: Sinus rhythm; P-R = 0.20 sec; QRS = 0.12 sec; left bundle branch block (Fig. 1).

Pulse Tracings: Jugular and hepatic tracings showed a normal pattern; no evidence of tricuspid insufficiency.

Phonocardiogram: Normal Q-1st interval. Short systolic murmur. Irregular, low-pitched diastolic rumble over the entire precordium. Split P_2. No opening snap (Fig. 2).

A subsequent tracing revealed a shorter diastolic rumble composed of large waves.

Electrokymogram of Left Atrium: Evidence of moderate mitral regurgitation.

INTERPRETATION OF FINDINGS

The patient was discussed at a Clinical Seminar. The diagnosis of rheumatic valvulitis was excluded because of the following data:

(1) Sinus rhythm and left bundle branch block. This combination is unusual in mitral stenosis.

(2) Diastolic murmur made of large waves recorded over a large surface of the precordium; normal Q-1st interval, no opening snap. These data are encountered in "functional" rumbles

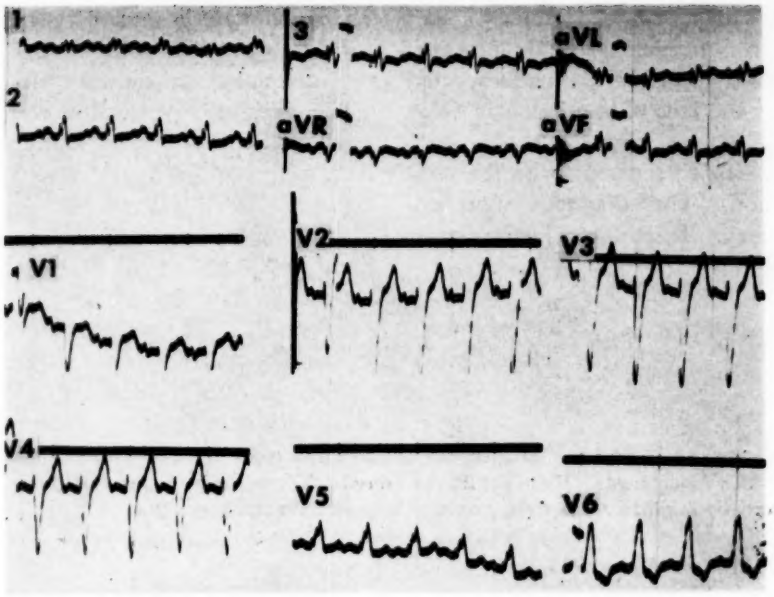


Fig. 1. Conventional electrocardiogram showing left bundle branch block.

simulating mitral stenosis. The splitting of P_2 was explained by the bundle branch block (so-called paradoxical splitting).

(3) Uniform dilatation of the heart without a sectional enlargement of the left atrium.

The diagnosis of *myocarditis, possibly viral,* was entertained.

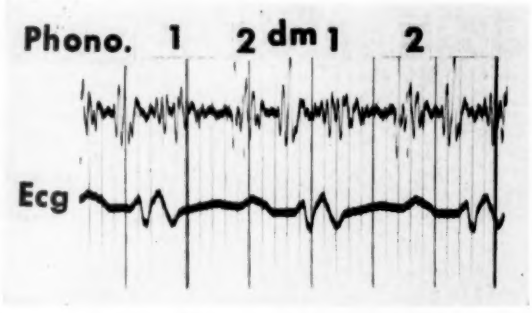


Fig. 2. Phonocardiogram showing faint systolic murmur and loud diastolic rumble (dm).

AUTOPSY FINDINGS

Anatomical diagnosis (Dr. H. Rappaport): Chronic myocarditis of unknown etiology, possibly viral. Chronic congestive failure.

DISCUSSION

Rheumatic heart disease with mitral stenosis usually presents a typical ECG pattern (double-peaked P_1 and P_2, diphasic P_3; right axis deviation; frequent evidence of right ventricular hypertrophy; possible right bundle branch block). In addition, these cases frequently have atrial fibrillation. Theoretically, pure mitral insufficiency of rheumatic etiology, through long lasting dilatation and hypertrophy of the left ventricle, could result in left bundle branch block and left ventricular strain. In such cases, however, the pattern of the atrial complex is similar to that of mitral stenosis indicating left atrial enlargement. This was absent in the present case.

Atrial septal defect may give rise to a "functional" diastolic rumble. It would produce a systolic pulmonic murmur, absent in this case; a tall, prominent P in V_1, also absent here; and—very likely—a right bundle branch block (either complete or incomplete). These data are basically different from those of the present case.

Coronary heart disease, due to arteriosclerosis, was unlikely (young age, female sex, no hypertension or diabetes, no history of acute episodes

of coronary insufficiency). Coronary heart disease due to unusual arterial processes (Buerger's disease, polyarteritis nodosa, etc.) was excluded by the lack of any lesion in other vascular areas.

Therefore, *myocarditis* seemed to be the most likely explanation. This diagnosis was confirmed by autopsy. Rheumatic heart disease was definitely excluded by autopsy. The episode which occurred at the age of 10 either was misdiagnosed or did not damage the heart. The existing myocarditis was definitely nonrheumatic (histological study).

A. A. Luisada, M.D.
M. R. Testelli, M.D.
Chicago, Illinois

Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original, all material submitted should have teaching value.

Coming in the May (Convention) Issue . . .

Aortic Stenosis . . . Cardiac Arrhythmias . . . Idiopathic Myocardial Hypertrophy

In Memoriam

Dr. Rudolph Matas (1860–1957)

"The bravest are the tenderest
The loving are the daring."

THE SOUTH has given to the medical world an enviable group of renowned physicians: McDowell, Beaumont, Long, and Gorgas. To this great lineage we now add one of its greatest, Dr. Rudolph Matas. He was born on Sept. 12, 1860 at Bonnet Carré, a small plantation in the Mississippi delta, not very far from New Orleans.

Catalonia, the proud birthplace of Ramon Lull, Enrique Monjo, and Pablo Casals, was also that of his parents. They came to settle in the land of DeSoto where the senior Dr. Matas practiced medicine. The family went to Spain, where the young Matas had his elementary education. They later returned to resettle in Texas and finally in the Magnolia State. In these two states the promising young man received his medical education. By special decree the University of Louisiana conferred upon him the degree of Doctor of Medicine before he had reached his twentieth birthday.

Not long after, Dr. Chaillé selected this brilliant and modest young doctor to aid him in the investigation of yellow fever, which was then ravaging Cuba and Louisiana. Their early contributions laid the necessary groundwork for the final conquest of this scourge by Drs. Reed and Gorgas. Dr. Matas' progress was so rapid that within a few years he was elevated to Chief of the Clinic of Surgery and Gynecology at Tulane University. His writings and accomplishments soon became known outside the state. With the death of Dr. Miles, the much sought after Chair of Surgery at Tulane was vacant. Some thought "new blood" was needed and looked northeast, in particular to Johns Hopkins, for the transfusion. "The Henry Clay of Medicine," Dr. Andrew W. Smyth, said: "It is nothing short of an outrage that the faculty of Tulane University should entertain the idea of going to Baltimore to fill the Chair made vacant by the death of Dr. Miles. Dr. Matas has genuine ability, which, in my judgment, is superior in many respects to genius itself. There is nothing that he teaches that he does not exhaust. I feel certain that the future will corroborate the opinion which I now express regarding Dr. Matas and any honor bestowed upon him will be justified by history." How prophetic were these words! Dr. Matas was made Professor of Surgery at thirty-four!

Fig. 1. A view of "Meo Domo," Dr. Matas' home in New Orleans.

He held this enviable Chair of Surgery until 1927 when he was sixty-seven.

While Director at Charity Hospital and the Medical School he introduced very many progressive innovations and reforms. It was during this period that Dr. Matas performed the first spinal anesthesia in this country. He also gave us a better approach to intestinal surgery, introduced intravenous use of saline solutions and perfected the Matas-Smyth pump for artificial respiration. His research in local, regional, and spinal anesthesia is well known. Incidentally, he was also the first to perform thyroid surgery in the state of Louisiana. The monumental and original work on *Aneurisms and Vascular Surgery* gained him the title of "Father of Vascular Surgery."

As a great organizer he was unsurpassed. He served as director of Base Hospital 34 Tulane Unit in France, 1916–17. Dr. Matas held so many positions that I am constrained to mention only a few. He was President of The New Orleans Medical and Surgical Society, American College of Surgeons, American Association of Thoracic Surgery, Southern Surgical Society, and The International Society of Surgeons, as well as being an Honorary Fellow of the American College of Cardiology. The vast number of decorations and honors he received are almost astronomical, extending as they did throughout Europe and the Western Hemisphere. This remarkable man received the world's highest award for general surgery, "The Henry Bigelow Medal" of the Boston Surgical Society. To climax all these awards, the world's highest award for Vascular Surgery was named in his honor.

The voluminous medical and historical writings are Oslerian both in style and diversification, very well justifying Dr. William Mayo's statement, "Dr. Matas is the most cultured physician in America." He worked to the very end completing the last volume of his encyclopedic medical history of Louisiana.

Dr. Matas was primarily a teacher; surger

Fig. 2. The original medallion, made by Dr. DeBellis in 1936, is now at the Rudolph Matas Memorial Library at Tulane University.

was secondary. His lectures include both the science and the art of surgery. He emphasized some salient attributes which go to make a true doctor. He would say, "The surgeon must be original. He must be endowed with the spirit of invention, must possess intuition to lead to untrod paths and discover new truths. He must be a gentleman at all times and cultivate compassion with tenderness, but not exclude firmness."

His dissertations on true and liberal education were veritable gems like those of Osler, his friend and admirer. He would say, "A surgeon must have coolness of nerve, clearness of judgment, and steadiness of hand for the emergency. He must be ever tender and have infinite patience with kind charity towards his fellow physicians." "De mortuis nil nisi bonum" did not completely satisfy him, but he would add, "de vivis nil nisi bonum."

Fortunate were his students to have had such an enthusiastic, stimulating and critical master; so progressive, provocative, and propagative. What an Herculean force shouldering behind the progress of medicine! He was one of the first to introduce Lister's concepts of aseptic technique in his operating room, and with a peculiar twinkle in his eye, would describe the early, crude methods of asepsis then employed; and would add, "We certainly have moved very fast in this field." As Sir Berkley Moynihan so well expressed it, "Modern aseptic surgery has made the operation safe for the patient; it is now the aim of the surgeon to make the patient safe for the operation." Incidentally, Dr. Matas received the honorary F.R.C.S., Eng. at the Lister Centenary in 1927.

If one should be fortunate enough to have read Dr. Matas' "Appreciation" in Halstead's two volume *Surgical Papers*, one cannot help but notice and feel the true noble character of this grateful doctor. Dr. Matas had lost one of his eyes while operating on a serious case of gonorrheal salpingitis; his eye became infected and he did nothing for it until the operation was over. It was Dr. Halstead, by the way, one of the "Big Four," who operated on this very young surgeon. The loss of his eye served as no handicap but rather as a stimulus. He achieved his greatest triumph with but one eye!

Instead of morning setting up exercises, he believed in mental exercises to keep the mind elastic, alert, and receptive for a better retentive memory. Of the many incidents which exemplify his phenomenal retentive memory this one has never been told. In 1931 Drs. F. Martin, J. Miller, George Stuart, and Matas were gathered in New York for the A.M.A. meeting. The Italian Medical Society invited these great men to commemorate Dr. Paolo DeVecchi. This rather unknown doctor had written a book, *Modern Italian Surgery*. As secretary of this society at that time, I read the book to fortify myself for any eventuality. When Dr. DeVecchi's name was mentioned to Dr. Matas he hesitated a moment then spoke of the book in such detail that I asked him, "When did you read it, Dr. Matas?" He answered, "When it was published by P. Hoeber in 1921." Ten years had passed and he remembered the contents better than I did. At this meeting Signor Orlando, who was visiting in New York, was also present. Dr. Matas, endowed as he was with the gift of many languages, carried on a fluent, prolonged conversation in Italian with the Italian Prime Minister.

On one of his many trips to New York, Dr. Matas suggested visiting the Museum of The Hispanic Society of America. I was delighted. What an opportunity for me to display my knowledge of art! Instead, he gave such a critical description of the paintings and related so many historical episodes about the artists, that a large listening group gathered around him thinking he was the curator. He kept on describing Goya, Mezquita, Zuloaga, Sorolla, and a multitude of others without noticing the large audience. We all had a good lesson in art.

Dr. Matas was a tireless and methodical worker. Unknown, except to very few of his close friends, he developed certain idiosyncrasies. For instance, he considered it a waste of time to lace shoes, therefore, he wore only Congress shoes. He used a snap-on tie instead of a bow tie or a Windsor knot. He always had three or four sharp pencils ready for use, like an artist with his brushes, ready to jot down his immediate impressions.

Music was his second choice in his life's desires.

Every time he came north we had to arrange a musical evening for him, opera or symphony. Toscanini was his favorite conductor. At recitals he would often whisper to me his comments on the conductor's interpretation of a particular passage. At times he would stay motionless in an all-absorbed pensive attitude and would suddenly be brought down to earth by the thunderous applause of the enthusiastic audience.

"Now at ninety," he said, "I cherish each year as though it were a precious jewel, because I don't know how many more I will get. I have frequently been asked of late how I manage to accumulate so many years. They say to me, 'Why, doctor, you look so well.' To this I reply that the thing to do is to just keep right on; to keep the flower of your enthusiasm well fed; to mix merry laughter with earnest labor; always to have some unfinished task which must not be either too much for your strength or too urgent to do. To kill time, is murder in the first degree."

We will miss this stimulating, zealous, inspiring teacher and kind and noble friend. This man personified the Latin graciousness and warmth, and the American progressive virility with the universality and equality of mankind. A true "Pater Hippocraticus." This kindly spirit reminds one of the beautiful phrase

"She walks in beauty like the night."

He also walked in beauty and humility like the morning sun with its tender warmth for all tranquil spirits who seek it. Humility, he would say, is a gift so rare in this competitive age of self-assertion and pointing finger. Humility is the foundation and mother of all virtues. He also strongly believed "When old age appears at the turning of the road, and one outgrows his usefulness, he should step aside and make room for the younger generation rather than to creep slowly backward into the cave of oblivion."

In 1926 after the Montreal meeting of the American College of Surgeons and the presentation of the Bigelow medal in Boston, the proud citizens and friends of Dr. Matas gave him a royal welcome home. This Mardi Gras city so well accustomed to festivities did the unusual. It went all out for this "Medical Hero" and reminded us of "Ritorna Vincitore" in Aida. Their love, esteem, and affection were genuine and spontaneous. They named him New Orleans' most distinguished citizen. The eulogies and tributes were long and many; and one of the most exquisite was this poem written by Jane Grey Rogers, Librarian at Tulane University.

The Soul of the Surgeon

He treads life's thoroughfare, where pain
And peace; want, plenty; joy, distress; all meet
And merge in fev'rish mis'ry at his feet,
Beseeching benediction—one long chain
Of human discord, which skilled hands must restrain
To tune anew to hope, until, replete
With music, 'neath transforming touch, full sweet
The broken keys sound pure, free tone again!
A master-player, his the Christlike part
Of speaking God's intention to His race;
Baptizing with fresh beauty blemished souls
And steering man's crushed courage, by love's chart,
To light divine, where health's refulgent grace
Heals shattered spirits seared by fleshly tolls.

He practiced and lived what he preached. Life for him was a long lesson in work and humility.

Dr. Matas, great teacher that he was, gathered the many broken pieces of knowledge and assembled them in such a way as to better aid us to achieve our final Samothrace.

Who seeks for heaven alone to save his soul
May keep the path, but will not reach the goal;
While he who walks in love may wander far,
But God will bring him where the Blessed are.
Henry Van Dyke

As he would end his affectionate letters to me. . .

"Arrivederci e sempre amico fedele"

So I end and say. . .

"Arrivederci mio caro maestro
Dio vi benedica."

Hannibal De Bellis, M.D., F.A.C.C.
New York, New York

Proceedings of the Ballistocardiograph Research Society*

Edited by SIDNEY R. ARBEIT, M.D., F.A.C.C.

Jersey City, New Jersey

President: ISAAC STARR, M.D. *Secretary:* DEWITT SMITH, M.D.

Influence of the Limbs on the Ballistocardiogram

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MODERN ballistic theory assumes the body to be a single mass elastically coupled to its support. Though this assumption holds at low frequencies, forces above 15 cps move body parts with respect to one another. Ballistocardiograms of four limbless adults were therefore used to: (a) evaluate distortion produced by disintegration of the theoretic "total body mass," and (b) to determine the physiologic role of the limbs in the genesis of the ballistocardiogram. All records were made with an ultra-low-frequency instrument as previously described. Subjects 1 and 2 were fully rehabilitated active young adults with complete traumatic amputation of both thighs. Patient 3 had congenitally absent lower extremities, a 3 cm left arm bud and a normal right arm. Patient 4 had complete ectromelia. This patient was a highly dependent individual who was not in a good state of physical training in contrast to the other three patients.

Frontal plane reaction force exceeded maximum normal in each limbless subject. This increase could not be explained by a change in force direction or balance or by the correction factor used to relate force to body size. Weighting the platform to simulate limb loading did not qualitatively or quantitatively reproduce the normal ballistocardiogram. The most striking morphologic abnormality was the presence of large diastolic vibrations at a frequency directly proportional to trunk length. These waves "rode in" to cancel or reinforce end systolic deflections. In patient 4, large complex pre-ejection waves were also present despite normal first heart sound and apex impulse. Representative records for each patient were shown and discussed.

The data support the view that the ballistocardiogram is originated by events anatomically close to the heart and that the elastically coupled limb masses distort whole body recordings. An ultra-low-frequency instrument sensing solely thoracic motion would therefore seem desirable.

* Interim meeting, October 27, 1957, Chicago, Illinois.

Ballistocardiogram in Abdominal Aortic Aneurysm. Follow-up on Case Presented at the Spring Meeting

ISAAC STARR, M.D.

Philadelphia, Pennsylvania

AT THE Spring meeting of the Society an unusual ballistocardiogram was presented and the members were requested to comment on it. This record, taken on the high frequency platform, showed as its chief abnormality a large abnormal wave following the J wave, and essentially similar to it in height. At this meeting one of the participants, I believe it was Dr. Samuel Talbot, raised the question whether the patient might have an aneurysm, but there was no clinical evidence of aneurysm at that time. However, shortly after the Spring meeting, in May 1957, an aneurysm of the abdominal aorta did manifest itself. This aneurysm increased rapidly in size and was eventually excised by the surgeon who replaced it by a graft. Most unhappily I was not informed about this operation and had no opportunity to get a ballistocardiogram on the subject after removal of the aneurysm. The man lived only a few months longer and then came to necropsy. The heart showed nothing of importance, so that the abnormality of the ballistocardiogram described above, must be attributed to the presence of the aneurysm.

Physical Efficiency, One of the Determinators of Ballistocardiographic Patterns

ERNST JOKL, M.D., F.A.C.C., AARNI KOSKELA, WILLIAM MCCUBBIN, ED.D., PETER JOKL, *and* SIDNEY R. ARBEIT, M.D., F.A.C.C.

From the Rehabilitation Center of the University of Kentucky, Lexington, Kentucky

THREE series of ten each direct body acceleration ballistocardiograms were presented. The first series was taken from outstanding participants in the 1957 NCAA track championship at Austin, Texas. The second series was from young, healthy, male students at the University of Kentucky. The third series was taken from Olympic and National athletic champions of 20 yrs or more ago.

The first series (tracings from active athletes) differs from the second, both in quality and quantity. The athletes had a mean resting pulse rate of 45 against 66 for the untrained Kentucky students. Amplitude of I wave was 7.1 vs. 4.5 mm; of J, 11.5 vs. 7.7 mm; of K, 12.3 vs. 8.7 mm. In the athletes there was virtually no respiratory amplitude variation. The college students' respiratory variation could be discerned in many cases. IJK time in athletes and non-athletes is almost the same, though diastole is much longer in the bradycardic athletes.

Roentgenkymographic studies show that in the resting heart of highly trained athletes, the systolic excursion of the lateral margin of the left ventricle is much smaller than in untrained subjects. However, when the athlete exercises, the amplitude becomes very large and the heart becomes smaller. The question is raised as to how in the absence of a good left ventricular excursion the pattern and force of the ballistocardiogram amplitude can be very high.

In ballistocardiograms from group 3, former athletes not now active, there is evident deterioration both in amplitude and normality of pattern. Most of the tracings are no longer amenable to quantitative analysis. In others amplitude is small and respiratory variations marked. Several of the ballistocardiograms in this series are distinctly abnormal.

In a previous study* we have shown that after four weeks of intensive physical training, the ballistocardiogram of a previously inactive 40-year-old man changed from a grade 3 to a grade 2. In another subject, a grade 1 tracing improved qualitatively within the range of normal variations previously presented by us. Accompanying the ballistocardiogram changes there were measurable increased physical performance capacities. This represents the reverse of changes found in the bcg of the athletes referred to above who had discontinued training.

This study points out that ballistocardiography can reveal significant differences between these three groups of subjects. A measurable cardiological determinant has thus been shown to correlate with physical efficiency. The assertions previously made by us that the ballistocardiogram appears to reflect variants of cardiovascular fitness within the range of the physiologic normal is thus supported.

Prediction of the Human Ballistocardiogram from a Plethysmographic Viewpoint

A. Noordergraaf, ph.d.,† H. W. Horeman, m.sc.,‡ S. P. ten Holt, m.d.,§ *and* R. van Dongen, b.sc.‡

From the Department of Therapeutic Research, the University of Pennsylvania School of Medicine, and the Department of Medical Physics under the direction of Dr. H. C. Burger, University of Utrecht

It was investigated whether the longitudinal movement of the center of gravity in man may be predicted from the physiologic events occurring in the ventricles, and in both the arterial trees. In order to calculate this movement the larger arteries were divided into 115 small segments with a total length of 667 centimeters. When m is the total mass of the body and the ballistocardiograph (less the excess masses of blood, i.e. the masses above the diastolic level in the ventricles and the arteries under study), and y the distance of its center of gravity to a reference plane through the center of the ventricles, while the excess masses in the segments are denoted by $m_1(t)\ldots,m_{115}(t)$, and their respective distances to the reference plane by $y_1,\ldots,y_{115}$, the position of the center of gravity of the system subject-ballistocardiograph $y_c(t)$ is given by

$$y_c(t) = \frac{my}{M} + \frac{m_1(t)y_1 + m_2(t)y_2 + \ldots m_{115}(t)y_{115}}{M}$$

The displacement of the center of gravity at any instant of time is determined by the second term in the right-hand member. To make the estimates, the distances were obtained from anatomic data, and the excess masses were calculated from normal pressure tracings. This calculation was carried out for each segment for time intervals of 20 milliseconds. Numerical integration of all these results at simultaneous time intervals, gives a curve which defines the movement of the center of gravity with time, and predicts the displacement ballistocardiogram. By differentiating these results we can

* Arbeit, S. R., Jokl, E., Koskela, A., and McCubbin, W. E.: Ballistocardiographic changes during a 30-day physical training period. *Am. Heart J.* 54: 57, 1957.

† Philadelphia, Pennsylvania.
‡ Utrecht, Holland.
§ Amsterdam, Holland.

also predict the *velocity* and *acceleration* (*force*) ballistocardiograms. The curves thus calculated can be converted into quantitative tracings of the movement of the body's center of gravity by dividing their amplitudes by the total mass of subject and ballistocardiograph M.

The general shape of the theoretic curves are quantitatively very similar to curves of displacement, velocity and acceleration secured from ultra-low frequency ballistocardiographs. The time relations to other events in the cardiac cycle, such as the heart sounds, are very similar also, and so we conclude that the record secured by ultra-low frequency ballistocardiographs is mainly due to the changes in the distribution of blood in the body as it leaves the ventricles and the pulse wave travels along the large arteries at each cardiac contraction.

The Beating of the Empty Heart*

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THE MAGNITUDE of body movement due to contraction of the heart under conditions where there is no ejection of blood is of importance in the problem of estimating stroke volume from pattern size.

To a first approximation a theoretical investigation of this problem can be made by setting up the equations of momentum and energy for the heart ejecting blood and for the same heart contracting under the same initial conditions but not ejecting blood. For the case of normal ejection these equations are:

$$M_B V_B = m_h v_h + m_b v_b \tag{1}$$

$$E - P = {}^1/_2 M_B V_B^2 + {}^1/_2 m_h v_h^2 + {}^1/_2 m_b v_b^2 \tag{2}$$

where M_B, m_h, and m_b represent respectively the mass of the body and ballistocardiograph, the mass of the heart and the mass of blood ejected, and V_B, v_h, and v_b the corresponding mean velocities during ejection. Also E represents the total energy available and P the portion transformed into pressure.

For the case of zero ejection the equations become

$$M_B V_B' = m_h' v_h' \tag{3}$$

$$E' - P' = {}^1/_2 M_B V_B'^2 + {}^1/_2 m_h' v_h'^2 \tag{4}$$

where V_B' and v_h' represent the mean velocities of body and ballistocardiograph and of heart respectively, and E' and P' are the total energy and the pressure energy.

The energy involved in the two cases can be related through equation

$$E' - P' = k(E - P) \tag{5}$$

so that where the kinetic energy involved in the two cases is the same the quantity k equals unity.

Simultaneous solution of these equations leads to

$$V_B'^2 = k \left[\frac{m_h'}{M_B + m_h'} \right] \times \left[\frac{M_B}{m_h} V_B^2 + \frac{m_b}{M_B} v_b^2 + \frac{m_b^2}{m_h M_B} v_b^2 - \frac{2 m_b}{m_h} V_B v_b \right] \tag{6}$$

which for the special case of the empty heart, where $m_h' = m_h$, reduces to

$$V_B'^2 = \left[\frac{k}{M_B (M_B + m_h)} \right] \times [M_B^2 V_B^2 + m_h m_b v_b^2 + m_b^2 v_b^2 - 2 m_b M_B V_B v_b] \tag{7}$$

Numerical solution of equation (7) using values of M_B, m_h, and m_b as 70,000, 500, and 200 g respectively leads to results illustrated in Figure 1. This figure indicates that for any

* This investigation was supported by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

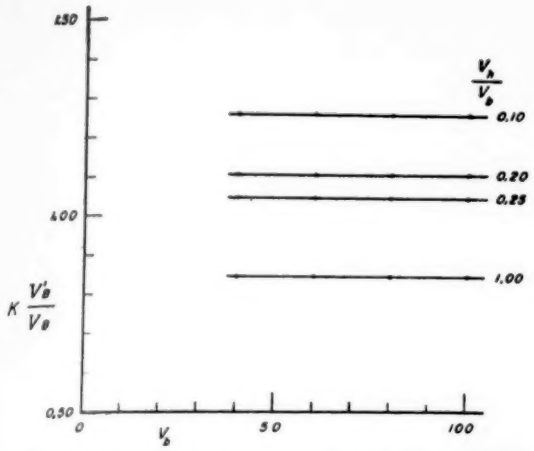

Fig. 1. Graphs showing relation of ratio of initial recoil velocity of the ballistic system during beating of the empty and normally ejecting heart (V_B'/V_B) to the ejection velocity (v_b).

specific ratio of heart velocity to blood velocity the ratio of the initial recoil velocity of the ballistic system during the beating of the empty heart to that occurring during the normally ejecting heart is independent of the ejection velocity and can be, on occasion, unity or greater. This means that the HI movement may not only not necessarily be reduced in magnitude from the normal to non-ejecting state but may be even increased depending on the value of k and also on the v_h to v_b ratio. This theoretic observation suggests that the HI portion of the ballistocardiogram may vary less in size with changes in stroke volume than the IJ portion which is more dependent upon circulating blood. An experimental observation of this sort was made in an early paper by the author.* "The most significant parallelism from the patient's records and the records of the model heart is the manner in which the J-wave increases much more markedly than the I-wave as the stroke volume returns toward normal."

It is not to be assumed, however, that these arguments invalidate the possible use of the ballistocardiograph in the estimation of stroke volume, since in actual life the variations of stroke volume are associated with corresponding variations in available energy at each ejected volume.

* Nickerson, J. L.: *J. Clin. Invest.* 28: 373, 1949

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

Postpartum Hypertension

FRANK A. Finnerty, Jr., Joachim H. Buchholz, and Robert L. Guillaudeu (Georgetown University Hospital, Washington, D. C.) recently studied data of 2,311 patients who delivered during the past four years and were followed in a toxemia clinic (*J.A.M.A.*, 165: 778, 1957). Serial studies on these patients revealed that 464 (20 per cent) showed the highest level of arterial pressure during the 3 to 17-week postpartum period. In 133 of these patients this represented the first appearance of hypertension. Their past history, pregnancy, delivery, and immediate postpartum period was entirely normal. Fifteen of these patients were hospitalized. Seventy-two hours bed rest caused only a 13 per cent reduction in mean arterial pressure. The response of the arterial pressure to ice, tilting, regitine, and histamine was not abnormal. Cardiac output and renal blood flow determinations were normal. In 331 patients there was a history of prior hypertension.

Further evidence for the existence of a pressor phenomenon during the postpartum period can be gained from serial studies on 30 patients followed through three pregnancies. The only elevations of arterial pressure in these patients occurred during the postpartum period. Four of this latter group are now being treated in the hypertensive clinic for persistent hypertension. In these four patients, it appeared that postpartum hypertension was the forerunner of hypertensive vascular disease. It would seem from these studies that a previously unrecognized pressor phenomenon, practically confined to multiparas, was active during the postpartum period. Since the condition is self-limited, therapy by drugs, restriction of activity or diet is not indicated.

Coronary Arteriography in Arteriosclerotic Disease of the Heart

DRS. Alan P. Thal, L. Stephen Richards, Richard Lester, and John Murray of the University of Minnesota report the following: Great advances in precise diagnosis and definitive therapy have followed the development of cerebral arteriography, aortography, and arteriography of the extremities. The blood vessels of the heart, however, have not yet been studied in coronary sclerosis of the living human. The following résumé outlines the technics and results in performing coronary arteriograms on thirty patients, many of whom had extremely advanced coronary sclerosis. The age range of this group of patients was from seventeen to seventy-six years.

All the patients with clinical coronary artery disease were carefully evaluated prior to arteriography. Initial studies were made under general anesthesia. Subsequently the arteriograms have been performed regularly under local anesthesia without untoward event. These patients were mildly sedated with 50 mg of

dramamine intravenously 30 minutes before the injection of contrast material and also 50 mg of demerol. Ten minutes before the procedure, $^1/_{100}$ gr of atropine was given intravenously. The brachial artery was exposed about two inches below the posterior axillary fold after the entire area had been infiltrated with 1 per cent procaine. An arteriotomy was made in the transverse axis of the vessel. This was of sufficient length to allow the insertion of a large catheter. In general, a #10 French thin-walled Lehman cardiac catheter was used. This was threaded through the brachial artery under fluoroscopic control and maneuvered into the ascending aorta. A right-sided approach has proved more successful. However, in three patients they were unable to insert the catheter into the ascending aorta. (At present, they are experimenting with the use of a controllable stylet to simplify the positioning of the catheter.)

At the conclusion of the procedure, the brachial artery was carefully resutured. In all cases, a good pulse was obtained at the wrist and there have been no complications. The catheter tip was positioned about 3 cm above the estimated position of the sinuses of Valsalva. Forty cm of Renografin® 76 per cent (Squibb) were injected in a period of 1.5 to 2 sec, using a pressure injection device. Originally the Rigler Watson Rapid Film Changer was used. Five exposures were made per sec. Exposure factors used were 400 to 500 milliamps, 95 kilovolts at $^1/_{30}$ or $^1/_{60}$ of a second. The patient's electrocardiogram was monitored throughout the injection phase and thereafter. During the injection the carotid arteries were compressed bilaterally. A trial of carotid compression was made prior to injection to identify patients with abnormally sensitive carotid sinus reflexes. No electrocardiographic signs of ischemia were seen. The biplane Shonander unit is being used, as arteriograms in one plane may be misleading.

Excellent visualization of the right main coronary, anterior descending, and circumflex branches of the left coronary artery was obtained in the majority of instances and several types of arterial disease have been delineated. In patients with angina decubitus, complete obstruction of one or more major coronary arteries was demonstrated uniformly. Localized strictures and areas of ectasia have also shown up clearly on the arteriograms. From the point of view of a direct surgical approach to the coronary arteries, it has been disappointing to find that even in young patients with severe angina decubitus the disease is diffuse in the majority of instances and not focal. Furthermore, in a single patient who demonstrated a nearly complete focal occlusion of the anterior descending artery, the symptomatology was so mild that operation could not under any circumstances be contemplated.

At the present time, these investigators are attempting to correlate the symptomatology, electrocardiographic changes and arteriograms in patients with varying degrees of coronary sclerosis. It has also been interesting to find an occasional patient with typical clinical symptoms of coronary disease who showed an entirely normal arterial system on arteriography. Perhaps one of the striking features of the study has been complete freedom from untoward sequela in this group of patients with severe heart disease.

Treatment of Acute Myocardial Infarction in Man with Cortisone

Robert A. Gerisch and Lucien Compeau (Harper Hospital, Detroit) used cortisone in the treatment of acute myocardial infarction in man after a careful study of its effect in experimentally produced infarcts in dogs. This revealed the following: (1) increased vascularity of the myocardium, (2) decreased mortality rate, (3) a smaller area of residual fibrosis, (4) fewer thromboses in the smaller vessels, and (5) a speedier recovery from a general anesthetic

than the control animals. These findings indicated that the primary action of cortisone was vascular (coronary and cerebral vasodilatation and peripheral vasoconstriction).

The following clinical study was undertaken. Thirty-eight cases of acute myocardial infarction were studied. Twenty-eight were treated with intramuscular cortisone for 10 days, using 300 mg the first day, 200 mg the second day, and 100 mg daily for the next eight days. Both treated and untreated patients usually revealed a drop in total circulating eosinophiles, sedimentation rate, and white blood count elevations, and a transient rise in fasting blood sugar. Twenty-five per cent (7 of 28) of the treated group died. In those also treated with dicumarol, the dicumarol requirement was slightly greater after cortisone was discontinued. Eight had some form of arrhythmia. Nineteen cases had associated shock and congestive failure. The mental attitude toward their illness was very good. There were no untoward effects attributable to cortisone therapy. Congestive failure was treated with the usual measures.

Although no conclusions could be reached relative to the mortality rate, it was concluded that there was a definite cortisone-like response in both the treated and control patients due to the infarction. Both experimental and clinical work indicates that both man and animal produce cortisone in response to a myocardial infarction. Some individuals are apparently not able to respond with enough cortisone production of their own, and therefore the administration of cortisone in the acute phase may be beneficial in (1) combating shock, (2) increasing collateral coronary circulation, (3) decreasing the size of the scar in the myocardium and, (4) improving the patient's mental attitude and protecting against associated cerebral manifestations which may be seen with myocardial infarction.

A Long-Acting Oral Quinidine Preparation

After the oral ingestion of a single dose of quinidine, its plasma level reaches a peak relatively quickly and then rapidly falls. Therefore, it is necessary to give multiple doses, even at night, to maintain an effective plasma level. For this reason, long-acting preparations have been sought.

Drs. Samuel Bellet, D. Finkelstein, and H. Gilmore (Philadelphia General Hospital) (*A. M.A. Arch. Int. Med.* 100: 750, 1957) describe their experience with a long-acting oral preparation of quinidine gluconate (Dura-Tab Quinidine Gluconate, Wynn Pharmacal Co., Philadelphia). Each tablet contained 330 mg of quinidine gluconate. They found that the effects of two daily doses of 1.0 g each, at a 10-hour interval (9 a.m. and 7 p.m.), were similar to those obtained with multiple oral doses of quinidine sulfate, in abolishing extrasystoles, atrial tachycardia, and atrial fibrillation. It appears that this preparation is worthy of further study.

Did you know that . . .

In the diagnosis of coarctation of the aorta, simultaneous palpation of the femoral and radial arteries may show almost pathognomonic findings. Normally, the femoral pulse is felt a fraction of a second earlier than the radial pulse. When coarctation is present the femoral pulse is felt a fraction of a second after the radial pulse. In addition, the femoral pulse will be weak and the blood pressure of the lower extremities will be lower than that of the upper extremities. This also is the reverse of normal.

* * *

In deciding on the advisibility of a cardiac operation for acquired or congenital heart disease, the mortality rate for the operation by the particular surgeon who will be doing the operation should not exceed 10 per cent. A mortality figure above this, makes the operation an experimental procedure. E. G.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Contraindications to Exercise Tests

Query: What are the contraindications to an exercise test in patients suspected of having coronary disease?

Answer: An exercise test for the purpose of confirming the diagnosis of coronary disease is contraindicated when (1) the clinical picture is definite, (2) the resting electrocardiogram shows significant abnormalities, (3) the patient is obviously ill, or (4) the recent onset of symptoms suggest the possibility of impending or actual myocardial infarction. While the Master "2-step" test has provided a useful measuring rod by which to judge the significance of electrocardiographic changes induced by standard exercise, the amount of stress for each patient must be carefully individualized. In elderly subjects, in patients whose capacity for exercise is unknown, and in those in whom coronary reserve may be seriously impaired, the least amount of exercise which affords a positive response should be the physician's objective. In such cases the routine application of a Master single ($1^1/_2$ min) "2-step" test followed by a double test (if the former results in a negative response) may be contraindicated because of the potential hazards. Unequivocal evidence of myocardial ischemia is not infrequently observed with considerably less or slightly more than the number of ascents and descents of the two-step staircase required in the performance of the single Master test.

Our group has performed many thousands of tests during the last 12 years in studies designed to evaluate the influence of coronary "vasodilator" drugs in patients with angina pectoris. Some of our patients have performed the double Master "2-step" test more than 500 times during this period. Despite the fact that many of our hundreds of patients had old myocardial infarctions and/or abnormal resting electrocardiograms we have not encountered a single accident attributable to the test procedure itself. All of our patients are instructed to stop the test if chest pain or pressure develops and nitroglycerine is kept ready for immediate use should such symptoms arise. Long experience has demonstrated that the exercise test, when performed by a well-qualified physician with due regard for the safety of the patient, has a definite place in the differential diagnosis of coronary insufficiency.

HENRY I. RUSSEK, M.D.
Staten Island, New York

Long-Term Anticoagulant Therapy

Query: What is the present status of long-term anticoagulant therapy in myocardial infarction?

Answer: Coronary artery thrombosis, the usual cause for myocardial infarction, results from an underlying atheromatous disease of the coronary intima and an incident of clot formation. Long-term or "permanent" anticoagulant therapy is directed toward preventing the superimposed thrombosis.

Such use of anticoagulants is widespread, but is by no means universal. Early use was confined to patients who had suffered one or more infarctions of the myocardium with the view to preventing additional episodes. More recent practice is to apply long-term therapy to patients with angina pectoris as well, hoping to reduce the incidence of the initial infarction. Anticoagulant drugs with long action are usually preferred because of the greater ease of maintaining a smooth level of therapeutic hypoprothrombinemia. Coumarin drugs, such as bishydroxycoumarin (dicumarol) and warfarin sodium (coumadin), and drugs of the phenindione group are in widest use.

Basic requirements for long-term anticoagu-

lant therapy are careful control by the physician, an intelligent cooperative patient and a dependable laboratory. In the absence of specific contraindications to the use of anticoagulants, the current program of therapy is reasonably safe.

Reported results of such therapy suggest a significant reduction of recurrent myocardial infarction and a striking reduction in death rate. Keyes, J. W., *et al.*, *Circulation* 14: 254, 1956) report a reduction of death rate of two-thirds in patients who have had one myocardial infarction and of four-fifths in patients who had previously suffered recurrent infarction. Owren's studies on angina pectoris patients in Norway (*Northwest Med.* 56: 298, 1957) suggest a reduction in death rate of one-third to two-thirds.

Worthy of consideration is an apparent increase in coronary accidents and deaths in groups where long-term therapy has been discontinued. Whether this is due in part to withdrawal effect of the drug or wholly to removal of protection from the patient cannot be stated at this time.

Col. B. E. Pollock, m.c.
Fitzsimons Army Hospital
Denver, Colorado

Diagnosis of Coronary Disease

Query: Can coronary artery disease be diagnosed before the appearance of symptoms or electrocardiographic findings? Are blood lipid studies of any value in this regard?

Answer: This question obviously points up a "gap" in cardiovascular disease diagnoses. In my opinion, it is rarely possible to make a diagnosis of coronary artery disease before the appearance of symptoms. Such a situation occasionally occurs when the "routine" examination of an asymptomatic individual produces an electrocardiogram absolutely diagnostic of a previous myocardial infarction (not merely ST and T wave deviations, but significant Q waves). This, in itself, infers that asymptomatic, that is, painless myocardial infarction does occur. On the other hand, it is a well established fact that a clinical diagnosis of coronary artery disease can be made even if the electrocardiogram is normal. In this respect, diagnostic electrocardiographic findings for coronary insufficiency may be produced by the use of standardized exercise. However, when both clinical symptoms and electrocardiographic findings (including those produced by standardized amounts of exercise) are absent, the physician's ability to make a diagnosis of coronary artery disease is very limited, perhaps impossible.

Many groups of investigators have presented data to prove that the concentration of various blood lipids (including cholesterol, cholesterol/phospholipid ratios, beta and alpha lipoproteins, cholesterol-uric acid-phospholipid indices, S_f flotation factors, chylomicrons, etc.) is abnormal in proven cases of coronary artery disease. On this basis, blood lipid studies have been proposed in order to predict the "proneness" of an individual to atherosclerosis and clinically manifest coronary artery disease. Attempts to consistently accomplish this in short range observations have been inadequate or nonconvincing. On the other hand, when an asymptomatic patient with a normal electrocardiogram but a strong family history of coronary artery disease has a high concentration of "abnormal lipids" in his blood serum, I do believe that one must be cautious in categorically denying the presence of asymptomatic atherosclerotic disease of his coronary arteries.

Seymoure Krause, m.d.
Pittsburgh, Pennsylvania

Book Reviews

An Atlas of Cardiac Surgery by Jorge A. Rodriguez, Saunders, Philadelphia, 1957, pp. 250, $14.00.

This atlas of cardiovascular surgery is a commendable illustrative review of the development of present day technics, written during a very difficult period in which the rapidity of transition of technics from closed methods and hypothermia to direct vision correction with the aid of extra-corporeal circulation has made it difficult even for the surgeon versed in this field to keep apace. Unfortunately, because of this rate of progress, books may become obsolete before they are published.

The excellent anatomical illustrations are of particular value to students and residents interested in the field of cardiovascular surgery, and are presented in a simplified manner, difficult to obtain elsewhere. Similarly, the illustrations of the surgical aspects of the many cardiovascular lesions now being surgically corrected are excellent.

The historical development of many of the technics is presented in a concise manner. I believe this atlas represents a valuable and informative adjunct to the paucity of surgical texts in this important field. EARLE B. KAY, M.D.

Pediatric Cardiology by Alexander S. Nadas. Saunders, Philadelphia, 1957, pp. 587, $12.00.

At the present time this book is the most comprehensive single text available on the subject of pediatric cardiology, encompassing rheumatic and congenital lesions as well as many other types of cardiac conditions encountered in pediatric practice.

Although a superficial description of the laboratory aids in diagnosis is included, e.g., cardiac catheterization, angiography, x-ray, electrocardiography and phonocardiography, the book is aimed primarily at the clinical level of diagnosis. In this respect it is ideal for the student as well as the practitioner of pediatrics and the extensive bibliography aids considerably as a reference for the more specialized pediatric cardiologist.

Basically the book is divided into four sections: *The Tools of Diagnosis*, *Acquired Heart Disease*, *Congenital Heart Disease*, and *Anesthesia for Children with Heart Disease*, each being relatively complete for a single volume such as this. In the first section there is an excellent discussion of the fundamentals of radiology, electrocardiography, and phonocardiography and presentation of basic information regarding cardiac catheterization and angiocardiography. In the section on congenital heart disease the lesions are categorized according to alterations in hemodynamics rather than on anatomical grounds or by the presence or absence of cyanosis. Instead of a stereotyped description of the signs and symptoms in the various cardiac lesions the abnormalities are discussed in relation to underlying physiological changes. The section on anesthesia provides an excellent reference for the pediatrician who must advise in the anesthetic management of cardiac children.

Controversial points are so stated and opinionated comments are likewise clearly indicated, thus enabling one to separate easily fact from theory. This, plus the numerous illustrations, tends to present quite clearly the various cardiac entities.

There is little doubt that this book is a "must" for any physician who deals with heart diseases in children. RAPHAEL N. PAUL, M.D.

Rhythmusstörungen des Herzens: Systematic, Ursache und klinische Bedeutung, Therapie by Konrad Spang. Georg Thieme Verlag, Stuttgart, 1957 (Intercontinental Medical Book Corporation, New York), pp. 548, plus atlas, pp. 111, $35.25.

More than 30 years ago the mechanism of the various disturbances of cardiac rhythm seemed obvious and in no need of further study. Repeatedly the present reviewer was advised to de-

vote himself to another field of research since the subject of cardiac arrhythmias was supposedly exhausted. Extrasystoles and paroxysmal tachycardias were explained by an increased excitability of the heart or parasystole (although a little thinking should have shown that both these explanations were not valid) and flutter as well as fibrillation were explained by circus mechanisms. Experimental and clinical data which contradicted these explanations were discarded and usually not even mentioned. Research concerning cardiac arrhythmias was scarce and editors of medical journals devoted to cardiac problems frankly stated that they were not interested in papers on cardiac arrhythmias.

Today we know that the mechanism of these disturbances encountered daily in our patients is still uncertain and in urgent need of further investigation. The same basic problems exist as did a generation ago.

Much work has been performed in the last decades. Since the classic monographs of Sir Thomas Lewis (1925) and of Wenchebach and Winterberg (1927) the available material has not been reviewed. This has been done now by Dr. Konrad Spang in an exemplary manner. Dr. Spang's book is based on a critical review of the international literature as well as his own vast experience. Aided by a fine collection of unusual and often unique clinical electrocardiographic tracings, the electrocardiogram, the mechanism, the clinical importance, and therapy of cardiac arrhythmias are discussed.

Preceding the main text are short discussions by Doerr of the morphology of the conduction system and by Trautwein of the physiology of cardiac arrhythmias.

In the 548 pages of text are included 109 illustrations. Two hundred twenty-eight electrocardiographic observations are reproduced in an enclosed atlas which can be handled separately, thus making perusal of the text much easier. The book is written in a simple, clear style with excellent correlation between text and figures. There is a subject index and a list of 1,708 critically selected references.

This is a standard work written with great critical objectivity. The discussions of many controversial issues, for instance, that of the mechanism of the Wolff-Parkinson-White (preexcitation) syndrome are masterly.

No one doing research on cardiac arrhythmias will be able to neglect this work; no one interested in this fascinating subject of irregularities of the heart beat will peruse this book without great profit. It is highly recommended.

DAVID SCHERF, M.D.

An Introduction to Electrocardiography by L. Schamroth. Thomas, Springfield, Ill., 1957, pp. 58, $2.50.

The need for a simple, concise presentation of the multiple complexities in electrocardiography is often disregarded. Schamroth's short book fills this need most adequately.

The manner of presentation and the simple yet very illustrative diagrams of the common electrocardiographic patterns capture the reader's interest.

This reviewer recommends this book as a potentially popular and useful guide for students and general practitioners.

SAMUEL A. WEISMAN, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. In so far as possible, as space permits, books of special interest will receive more extensive reviews.

The Physician's Own Library by Mary Lou Marshall, Thomas, Springfield, Ill., 1957, pp. 87, $3.00.

Digitalis, edited by E. Grey Dimond, Thomas, Springfield, Ill., 1957, pp. 225, $7.00.

A Primer for Coronary Patients by Robert J. Needles and Edith M. Stoney, Appleton-Century-Crofts, New York, 1958, pp. 176, $3.75.

Heart Disease and Pregnancy—Physiology and Management by C. Sidney Burwell and James Metcalfe, Little, Brown and Co., Boston, 1958, pp. 338, $10.00.

Low-Fat Cookery by Evelyn S. Stead and Gloria K. Warren, McGraw-Hill, New York, 1956, pp. 184, $3.95.

Die Lungenarterienbahn bei angeborenen Herzfehlern by Kurt Köhn and Marianne Richter, Georg Thieme Verlag, Stuttgart, pp. 112, D.M. 29.50 (approx. $7.00).

College News

Seventh Annual Meeting

GENERAL CONVENTION SCHEDULE

Chase-Park-Plaza Hotel, St. Louis, Mo., May 20 to 24, 1958

May 19 through May 24—Press and Publicity—Pony Express Room—Chase—Lobby Floor
May 20 through May 24—Ladies' Hospitality Room—Georgian Room—Park Plaza
May 20 (Noon–5 P.M.)—Set up Exhibits—Exhibit Hall—Chase
May 20 (6 P.M.—Midnight)—82nd Board of Trustees—Lido Room—Chase—Lobby Floor

Wednesday, May 21

8 A.M.–6 P.M.—*Registration*—Exhibit Hall
9 A.M.–6 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
10 A.M.–Noon—1st Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon–2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
Noon–2 P.M.—Board of Governors' Luncheon Meeting—Colonial Room—Chase—2nd Floor
2–5:30 P.M.—2nd Scientific Session—Khorassan Room—Chase—Lobby Floor
6–6:45 P.M.—Reception—Tiara Lounge—Park Plaza—20th Floor
6:45–8 P.M.—Dinner—Tiara Room—Park Plaza—20th Floor
8–10 P.M.—Fireside Conferences—Tiara Room—Park-Plaza—20th Floor

Thursday, May 22

9 A.M.–5 P.M.—*Registration*—Exhibit Hall
9 A.M.–5 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
9 A.M.–Noon—3rd Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon–2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
1:30–3:30 P.M.—4th Scientific Session—Khorassan Room—Chase—Lobby Floor
4–5:30 P.M.—7th Annual Business Meeting—Starlight Roof—Chase
6–6:45 P.M.—Cash Bar—Zodiac—Chase
6:45–8:15 P.M.—Buffet—Starlight Roof
8:30–10:30 P.M.—Convocation: Honorary Fellowships and Presentation of the Groedel Medal—Groedel Memorial Lecture—Khorassan Room—Chase—Lobby Floor

Friday, May 23

9 A.M.–5 P.M.—*Registration*—Exhibit Hall
9 A.M.–5 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
9 A.M.–Noon—5th Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon–2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
2–5:30 P.M.—6th Scientific Session—Khorassan Room—Chase—Lobby Floor
6:30–7:30 P.M.—Reception and Cocktails—Khorassan Room—Chase—Lobby Floor
7:30–9:30 P.M.—Seventh Annual Banquet—Khorassan Room—Chase—Lobby Floor
9:30–10:30 P.M.—Professional Entertainment—Khorassan Room—Chase
10:30–Midnight—Dancing—Khorassan Room—Chase—Lobby Floor

Saturday, May 24

9 A.M.–1 P.M.—*Registration*—Exhibit Hall—Chase
9 A.M.–1 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
9 A.M.–Noon—7th Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon to 2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
1:30–5 P.M.—8th Scientific Session—Khorassan Room—Chase—Lobby Floor
5 P.M.—Official Closing of the Convention
5–11 P.M.—83rd Board of Trustees Dinner Meeting—Lido Room—Chase—Lobby Floor

SCIENTIFIC PROGRAM

Chairman: JOHN S. LA DUE, M.D., F.A.C.C.

First Scientific Session

Wednesday, May 21, 1958, 10 A.M. to Noon

Symposium on
INFARCTION AND THROMBOEMBOLISM

Chairman: EDWARD MASSIE, M.D., F.A.C.C.
Director of Cardiovascular Clinic, Washington University and Director of Heart Station, Jewish Hospital, St. Louis, Mo.

1. Electron Microscopic Studies of Early Stages of Experimentally Produced Myocardial Infarction.
   RICHARD E. BRYANT, A.B. and ROBERT M. O'NEAL, M.D.
   Department of Pathology, Washington University School of Medicine, St. Louis, Mo.
   Discussion to be opened by JOHN R. SMITH, M.D.

2. Experiences with Fibrinolytic Therapy in Patients with Acute Myocardial Infarction.
   ANTHONY P. FLETCHER, M.D., NORMA ALKJAERSIG, M.S., FOTUS E. SMYRNIOTIS, M.D., and SOL SHERRY, M.D.
   Department of Medicine, Jewish Hospital, St. Louis, Mo.
   Discussion to be opened by JOHN S. LA DUE, M.D.

3. Mechanism of Pulmonary Infarction.
   JOHN R. SMITH, M.D.
   Department of Medicine, Washington University School of Medicine, St. Louis, Mo.
   Discussion to be opened by KENNETH C. PRICE, M.D.

4. Dietary Production of Myocardial Infarction.
   WILBUR A. THOMAS, M.D., W. STANLEY HARTROFT, M.D., and ROBERT M. O'NEAL, M.D.
   Department of Pathology, Washington University School of Medicine, St. Louis, Mo.
   Discussion to be opened by RICHARD J. BING, M.D.

Second Scientific Session

Wednesday, May 21, 1958, 2 to 5:30 P.M.

Symposium on
EFFECT OF STRESS AND ENVIRONMENT ON CARDIAC FUNCTION

Moderator: ERNST JOKL, M.D., F.A.C.C.
Professor of Physiology, Kentucky Rehabilitation Center, University of Kentucky, Lexington, Ky.

1. Physiology and Methods of Evaluation.
   ROBERT P. GRANT, M.D., F.A.C.C.
   National Heart Institute, Bethesda, Md.

2. Sudden Collapse and Death Following Physical Stress.
   ERNST JOKL, M.D., F.A.C.C.
   Professor of Physiology, Kentucky Rehabilitation Center, University of Kentucky, Lexington, Ky.

3. Environmental Aspects.
   CAPT. ASHTON E. GRAYBIEL, M.C., F.A.C.C.
   Naval Air Station, Pensacola, Fla.

4. Exercise in Patients with Heart Disease.
   SAMUEL FOX, III, M.D.
   National Heart Institute, Bethesda, Md.

5. Cardiac Stress as a Problem in Industrial Medicine.
   G. W. H. SCHEPERS, M.D., F.A.C.C.
   Institute of Industrial Health, University of Michigan Medical School, Ann Arbor, Mich.

6. Panel Discussion: To be opened by ALFRED D. DENNISON, M.D., F.A.C.C.

Fireside Conferences

Wednesday, May 21, 1958, 8 to 10 P.M.

1. Phonocardiography as an Office Procedure.
   ALDO LUISADA, M.D., F.A.C.C.
   Associate Professor of Medicine and Director, Division of Cardiology, Chicago Medical School and Mount Sinai Hospital, Chicago, Ill.

2. Surgical Treatment of Acquired Heart Disease.

DWIGHT E. HARKEN, M.D., F.A.C.C.
Associate Clinical Professor of Surgery, Harvard Medical School; Surgeon, Peter Bent Brigham Hospital, Boston, Mass.

3. Surgical Treatment of Acquired Heart Disease.
CHARLES P. BAILEY, M.D., F.A.C.C.
Professor of Surgery, Hahnemann Medical School, Philadelphia, Penna.

4. Pulmonary Embolism.
D. W. CHAPMAN, M.D.
Baylor University College of Medicine, Houston, Tex.

5. Sodium and Potassium Metabolism in Heart Disease.
GEORGE B. MENEELY, M.D., F.A.C.C.
Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

6. Traumatic Heart Disease.
JAMES C. DRYE, M.D.
Associate Professor of Surgery, University of Louisville, Louisville, Ky.

Third Scientific Session

PRESENTATION OF SCIENTIFIC PAPERS BY MEMBERS

Thursday, May 22, 1958, 9 A.M. to Noon

Chairman: ALDO A. LUISADA, M.D., F.A.C.C.
Division of Cardiology, Chicago Medical School and Mount Sinai Hospital, Chicago, Ill.

1. Comparison of Clinical and Hemodynamic Results of Mitral Commissurotomy One to Three Years After Surgery.
PAUL KEZDI, M.D., F.A.C.C. and HANS WESSEL, M.D.
The Cardiovascular Laboratory, Wesley Memorial Hospital and Department of Medicine, Northwestern University Medical School, Chicago, Ill.

2. Initial Ultra-Low Frequency BCG Complexes in Major Arterial Obstruction.
JAN NYBOER, M.D., F.A.C.C. and ROONEY WILLARD, M.D.
Department of Cardiovascular Physiology, Harper Hospital, Detroit, Mich.

3. External Phonocardiogram Compared with Intracardiac Phonocardiogram in Atrial Septal Defect.
C. K. LIU, M.D., F.A.C.C. and A. JACONO, M.D.
Division of Cardiology, Chicago Medical School and Mount Sinai Hospital, Chicago, Ill.

4. The Value of Newer Roentgenographic Dye Study Technics in the Analysis of Acquired Cardiovascular Disease.
WILLIAM LIKOFF, M.D., F.A.C.C. and JOSEPH F. URICCHIO, M.D.
Division of Medicine, Bailey Thoracic Clinic, Philadelphia, Penna.

5. The Alveolar Hypoventilation Syndrome; A Rare Cause of Heart Failure.
RALPH E. SMITH, M.D., JAMES L. BROWN, M.D., and WAYNE HOSETH, M.D.
Cardiovascular Disease Section, Veterans Administration Hospital, and Department of Medicine, University of Minnesota, Minneapolis, Minn.

6. The Successful Use of Induced Hypometabolism for the Elimination of Arrhythmias in the Euthyroid Patient.
ELIOT CORDAY, M.D., F.A.C.C., HENRY L. JAFFE, M.D., HERBERT GOLD, M.D., and JOHN H. WILLIAMS, M.D.
Department of Medicine, Radiology and Radiation Therapy, Cedars of Lebanon Hospital and University of California School of Medicine, Los Angeles, Calif.

7. A Clinical Study of Internal Mammary Ligation for Angina Pectoris with Sham Operations.
E. GREY DIMOND, M.D., F.A.C.C., C. F. KITTLE, M.D., J. E. CROCKETT, M.D., and L. M. RODRIGUEZ, M.D.
Department of Medicine and Surgery, University of Kansas School of Medicine, Kansas City, Kan.

Fourth Scientific Session

Thursday, May 22, 1958, 1:30 to 3:30 P.M.

Symposium on
MYOCARDIAL METABOLISM

Moderator: RICHARD J. BING, M.D., F.A.C.C.
Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

1. Anerobic and Aerobic Metabolism.
   JOHN GERLEGY, M.D., PH.D.
   Established Investigator, American Heart Association; Associate Biochemist, Massachusetts General Hospital, Boston, Mass.

2. Effect of Heart Disease.
   RICHARD J. BING, M.D., F.A.C.C.
   Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

3. Effects of Cardiac Glycosides.
   GEORGE H. ACHESON, M.D.
   Professor of Pharmacology, University of Cincinnati College of Medicine, Cincinnati, Ohio.

4. Panel Discussion.

GROEDEL MEMORIAL LECTURE ON HUMANITIES IN MEDICINE

Thursday Evening, May 22, 1958

THE CHANGING PATTERNS OF DISEASE
PAUL A. CANNON, M.D.
Emeritus Professor of Pathology, University of Chicago Medical School, Chicago, Ill.

Fifth Scientific Session

Friday, May 23, 1958, 9:00 A.M. to Noon

Symposium on
SOME COMMON DRUGS USED IN THE TREATMENT OF HEART DISEASE

Moderator: JOHN H. MOYER, M.D., F.A.C.C.
Professor of Medicine, Hahnemann Medical School, Philadelphia, Penna.

1. Clinical Use of Cardiac Glycosides.
   E. GREY DIMOND, M.D., F.A.C.C.
   Professor and Chairman, Department of Medicine and Director of Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City, Kan.

2. Clinical Use of Quinidine.
   REUBEN BERMAN, M.D., F.A.C.C.
   Associate Professor of Clinical Medicine, University of Minnesota School of Medicine, Minneapolis, Minn.

3. Diuretics.
   WALTER A. MODELL, M.D.
   Associate Professor of Pharmacology, Cornell University Medical College, New York, N. Y.

4. Monamine Oxidase Inhibitors.
   ALBERT SJOERDSMA, M.D.
   National Heart Institute, Bethesda, Md.

5. Hypotensive Agents.
   JOHN H. MOYER, M.D., F.A.C.C.
   Professor of Medicine, Head of Department of Medicine, Hahnemann Medical School, Philadelphia, Penna.

Sixth Scientific Session

Friday, May 23, 1958, 2 to 5:30 P.M.

Symposium on
SOME COMMON DRUGS USED IN THE TREATMENT OF HEART DISEASE (CONCLUSION)

6. Panel Discussion.

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CONVENTION GUEST LECTURE

4 to 5:30 P.M.

Chairman: GEORGE R. MENEELY, M.D., PRESIDENT OF THE COLLEGE

LONG TERM USE OF ANTICOAGULANTS
IRVING S. WRIGHT, M.D.
Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y.

Discussion to be opened by
BENJAMIN MANCHESTER, M.D., F.A.C.C.
Washington, D. C.

* * *

Seventh Scientific Session

Saturday, May 24, 1958, 9 A.M. to 12 Noon

Symposium on
MODERN MANAGEMENT OF TETRALOGY OF FALLOT

Moderator: J. MAXWELL CHAMBERLAIN, M.D., F.A.C.C.
Director of Thoracic Surgery, Roosevelt Hospital, New York, N. Y.

1. Selection of Patients and Time for Surgery.
   WILLIAM LIKOFF, M.D., F.A.C.C.
   Associate Professor of Medicine, Hahnemann Medical School, and Chief, Division of Cardiology, Bailey Thoracic Clinic, Philadelphia, Pa.

2. The Place of the Blalock Procedure.
   DWIGHT C. MCGOON, M.D.
   Division of Surgery, Mayo Clinic, Rochester, Minn.

3. The Status of the Potts Procedure.
   CLARENCE CRAFOORD, M.D.
   Professor of Thoracic Surgery, Karlinska Sjukhus, Stockholm, Sweden.

4. The Status of the Brock Procedure.
   SIR RUSSELL BROCK
   Chief Surgeon, Brompton Hospital, London, England.

5. The Definitive Operation—Open Heart Procedure.
   C. WALTON LILLEHEI, M.D., F.A.C.C.
   Professor of Surgery, University of Minnesota, Minneapolis, Minn.

6. Physiologic Changes Following Surgery for Tetralogy of Fallot.
   C. RAWLINS HANLON, M.D.
   Professor of Surgery and Director of Department of Surgery, St. Louis University School of Medicine, St. Louis, Mo.

7. Panel Discussion.

Eighth Scientific Session

Saturday, May 24, 1958, 1:30 to 5 P.M.

Symposium on

THE SURGICAL MANAGEMENT OF THE AORTIC VALVE

Moderator: IVAN BARONOFSKY, M.D.
Director of Surgery, Mount Sinai Hospital and Clinical Professor of Surgery, Columbia University, New York, N. Y.

1. Selection of Patients for Surgery.
   THOMAS H. BURFORD, M.D.
   Professor of Surgery, Washington University School of Medicine, St. Louis, Mo.

2. Aortic Valvulotomy (Transventricular).
   ROBERT P. GLOVER, M.D., F.A.C.C.
   Director, Cardiovascular Research Laboratory and Chief of Thoracic and Cardiac Surgery, Presbyterian Hospital, Philadelphia, Penna.

3. Aortic Valvulotomy (Transaortic).
   DWIGHT E. HARKEN, M.D., F.A.C.C.
   Associate Clinical Professor of Surgery, Harvard Medical School and Chief of Thoracic Surgery, Peter Bent Brigham and Mt. Auburn Hospitals, Boston, Mass.

4. Aortic Valvulotomy (Retrograde Coronary Sinus Perfusion).
   C. WALTON LILLEHEI, M.D., F.A.C.C.
   Professor of Surgery, University of Minnesota, Minneapolis, Minn.

5. Aortic Valvulotomy (Cardiac Arrest).
   DONALD B. EFFLER, M.D.
   Associate Professor of Thoracic Surgery, Frank E. Bunts Institute, Cleveland, Ohio.

6. Panel Discussion.
   Panel to be joined by F. JOHN LEWIS, M.D.
   Associate Professor of Surgery, Northwestern University Medical School, Chicago, Ill.

Committees for the Convention

SEYMOUR FISKE, M.D., F.A.C.C.

SCIENTIFIC PROGRAM COMMITTEE

JOHN S. LA DUE, Chairman, *New York, N. Y.*, J. Maxwell Chamberlain, *New York, N. Y.*, Simon Dack, *New York, N. Y.*, E. Grey Dimond, *Kansas City, Kan.*, Robert Grant, *Bethesda, Md.*, Arthur C. Guyton, *Jackson, Miss.*, Dwight E. Harken, *Boston, Mass.*, Aldo A. Luisada, *Chicago, Ill.*, Edward Massie, *St. Louis, Mo.*, Dale P. Osborn, *Cincinnati, Ohio*, and Myron Prinzmetal, *Beverly Hills, Calif.*

General Convention Chairman

LOCAL ARRANGEMENTS COMMITTEE—ST. LOUIS

EDWARD MASSIE, Chairman, Morris Alex, Malcolm B. Bawell, Richard J. Bing, Donald W. Bussman, Mary A. Davis, Julius Elson, James G. Janney, Sidney Jick, Chester Lynxwiler, J. F. Gerard Mudd, John J. Nuetzel, Charles Silverberg and Thomas J. Walsh.

SCHEDULE OF SOCIAL FUNCTIONS FOR THE LADIES

A special entertainment for the ladies will be provided during the convention of the American College of Cardiology in St. Louis, Missouri, May 21–24, 1958. Luncheons, a Fashion Show, and visits to historical and cultural centers have been arranged in the three-day program.

The cost is extremely modest, about $4.00 per day, per person. Please make advance reservations as early as possible to insure adequate preparations for all who wish to attend. For reservations please contact: Mrs. Julius Elson, Chairman, 5 Granada Way, La Due 24, Missouri.

Wednesday—May 21, 1958, 12 Noon–4:55 P.M.

Luncheon at Frontier Room of Montclair Apartments, 12 Noon.

Bus trip, 1 P.M., with visits to Jefferson Memorial, Museum of Fine Arts and the Zoo in Forest Park, and The Jewel Box, returning to Chase Hotel by 4:55 P.M.

The Frontier Room of the Montclair is noted for very fine food, especially Cantonese dishes. You will be served a Cantonese lucheon for $1.50 per person. The Montclair is just two short blocks from the Chase Hotel.

The Jefferson Memorial is located in Forest Park and was built during the time of the St. Louis Exposition. The Missouri Historical Society has taken it over and has many fascinating exhibits, including Indian relics and Missouri historical relics in the East wing of the building. The West wing houses the trophies and gifts received by Charles Lindbergh after his historic trans-Atlantic flight in 1927.

The Art Museum is located in beautiful Forest Park, top of Art Hill, and overlooks miles of the park. It is ranked as one of the four best in all of the United States. The museum's collection of Chinese bronze, ceramics, and paintings is world famous. A guided tour has been arranged.

St. Louis Zoo, 700 acres of park, features numerous unusual animals. A monkey show is scheduled.

The Jewel Box is aptly named as it does, indeed, look like a huge jewel box. Breathtakingly beautiful flowers are exhibited in the completely glass constructed showcase building. Soft organ music is played during the day.

Thursday—May 22, 1958, 10 A.M.–4:10 P.M.

Shaw's Garden is modeled after Kew Gardens and, many say, equally beautiful. There are 75 acres of trees and plants, more than 12,000 species. Winter flowering shrubs are in the Linnean House, only remaining greenhouse built in the lifetime of Henry Shaw who established the Garden in 1858. It is one of the few 19th century greenhouses in the country, has intricate fanlights and less glass than the more modern houses. Tropical lily ponds with pink, blue, and unusual hybrid water lilies, the world's rarest orchids, magnolias, palms, orange, and banana trees are shown there.

Grant's Farm was once owned and occupied by General U. S. Grant. Now owned by Anheuser-Busch it is the present home of August Busch. You will be taken on a tour of the farm and will see Mr. Busch's unusual collection of animals. The tour takes one and one-half hours and at the end of the tour refreshments will be served.

Friday—May 23, 1958, 10 A.M. –2:30 P.M.

Board buses at Chase hotel 10:00 A.M., visit to Campbell House followed by scenic ride along Mississippi River Front to see the Old Cathedral, Old Court House, and Eugene Field Home. A special luncheon and Fashion Show have been arranged at the Stix-Baer-Fuller Department Store. Afternoon will be free for shopping or bus may be taken back to Chase Hotel at 2:30 P.M.

The Campbell House is among the most historic buildings still standing in St. Louis. A narrow, three-story, gray painted brick building with stable summerhouse and wrought-iron fence, it is the last of the mansions that made Lucas Place the fashionable residential district in the ante-bellum period. Robert Campbell, an Irish fur trader, was a business leader of St. Louis for many years. The house was preserved intact and the furnishings are as they were when Mr. Campbell lived there. Everything is authentic, including the costumes of mid-Victorian period.

The Old Cathedral has been church property throughout the history of St. Louis. The first Mass was held there in 1764. The present building, fourth on the site, was completed in 1834.

The Old Court House is a Greek-revival building where much of the history of the Mississippi valley was written. The famous Dred Scott case had its beginning in one of the courtrooms and slaves were once auctioned from the steps on the east side.

The Eugene Field House, built about 1845, is a three-story red brick house where Eugene Field spent his boyhood.

Stix-Baer-Fuller is one of the country's leading department stores. A Fashion Show of new summer clothes will take place while luncheon is served there. Following luncheon, guests may see the exhibit of satellites in the Founder's Room or go shopping.